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THIOURACIL IN THE TREATMENT OF THYROTOXICOSIS*

A Report of Seventy-Two Cases

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IN THYROTOXIC patients thiouracil has been found to cause a lowering of the metabolic rate to normal levels, a return to normal of the protein-bound iodine of the plasma and concurrently a clinical remission of the disease.[1, 2] The evidence accumulated suggests that these changes result from the action of the drug on the thyroid gland, decreasing in some manner the formation of its hormone. Since the appearance of the above reports we have used thiouracil§ in the treatment of 72 thyrotoxic patients, including a continuation of treatment of the 9 patients reported by Williams and Bissell.[2] In the course of these studies a number of observations were made concerning the progress of the disease as influenced by prolonged treatment with thiouracil, the desired dosage, the complications arising from the use of the drug, the use of thiouracil instead of iodide preoperatively and the production by thiouracil of certain anatomic and chemical changes in the thyroid gland.

The present series includes all the patients with thyrotoxicosis seen since the beginning of the study. A number of variations in the disease were found. There were examples of classic Graves's disease, toxic nodular goiter and toxic adenoma. The duration of the illness varied from three weeks to twenty-two years. Subtotal thyroidectomies had previously been performed on 13 patients. In one case this operation had been carried out three times, and in another twice. Thirteen patients had taken potassium iodide for several weeks, discontinuing it within about a month before thiouracil therapy was begun. Most of the patients were not hospitalized for more than one day. Complete physical examinations were made, particular attention being paid to the size, configuration and consistency of the thyroid gland and to the manifestations of exophthalmic ophthalmoplegia. Before the beginning of treatment an adequate number of determinations of the basal metabolic rate were made to indicate the degree of toxicity.

In the first 30 patients treated the initial daily dosage of thiouracil was usually 1 gm., but with subsequent patients it was 0.6 gm. daily or rarely 0.4 gm. In most cases, however, the dosage was reduced to 0.2 gm. daily over a period of about six weeks. Single doses usually consisted of 0.2 gm., although they were sometimes only 0.1 gm. When several doses were given daily, they were spaced evenly throughout the day for reasons that will be discussed later.

Almost all the patients were permitted to perform their usual duties but were asked to return to the outpatient clinic at the Boston City Hospital for observation, including a determination of the basal metabolic rate, at intervals of one or two weeks during the first six weeks of treatment, and at intervals of about four weeks thereafter. The white-cell count was usually made several times during the first six weeks, but thereafter only when the patient developed some type of infection or complained of vague weakness and malaise.

We have now treated 48 patients for more than two months, 35 for more than four months, and 16 for more than six months. Twenty-four patients have been treated for two months or less.

RESULTS OF TREATMENT

Although estimations of the clinical status of the patients were made at each visit, the thyrotoxicity can best be demonstrated by presenting the rates of basal oxygen consumption, since the results of this test were usually in accord with the observed clinical changes. Many patients maintained that a marked improvement had occurred within twenty-four to forty-eight hours after first taking thiouracil. This rapid change may have been due in part to a

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§The thiouracil was supplied through the courtesy of the Lederle Laboratories, Incorporated, Pearl River, New York.

mild sedative effect of the drug, as well as to its psychologic effects.

Changes in Basal Metabolic Rate

There were 59 patients who had not received iodide treatment for more than one month before thiouracil was started and were therefore probably free of iodide effect. These cases were divided into three groups according to whether the lowest metabolic rate preceding thiouracil treatment was from +55 to 89, from +35 to 55 or from +15 to 35 per cent; there were 16, 23 and 20 patients, respectively, in each division. For each group was calculated an average of the basal metabolic rates obtained before and after thiouracil treatment and at equal intervals thereafter. These results are plotted in Figures 1, 2 and 3, together with the extreme variations in the metabolic rates and the average

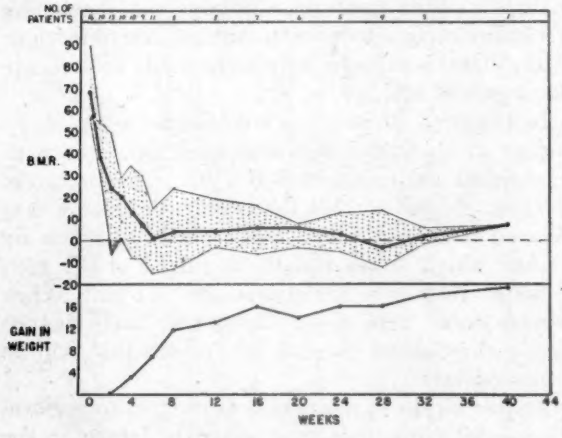

FIGURE 1. *The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 16 Patients with Marked Thyrotoxicosis.*

weight gain. In these figures are included the results obtained preoperatively in 18 patients who had a subtotal thyroidectomy. One patient felt so well after a few months of treatment that he refused any more treatment or examination. Four patients discontinued therapy for intervals of two to four weeks, and 3 of these had a slight recurrence of their disease. All these patients had a normal basal metabolism for more than a month before discontinuing treatment. One patient discontinued therapy for three weeks after having taken it for two months, but there was no relapse. Therapy was resumed; a few months later she discontinued it for one month and experienced a recurrence of the disease, but there was no thyrotoxicity within three weeks after resuming treatment. Another patient discontinued therapy after three months and experienced a relapse in three weeks; complete remission did not occur until six weeks after resuming treatment. A third patient stopped taking the drug after seven months. An exacerbation was observed in two weeks, and the metabolic rate was not found normal until four weeks after resuming treatment. The metabolic rates during the exacerbation in these 3 patients have been omitted, but those obtained after a few weeks of resumed treatment are included.

The basal metabolism decreased under thiouracil treatment much more rapidly in the severe cases

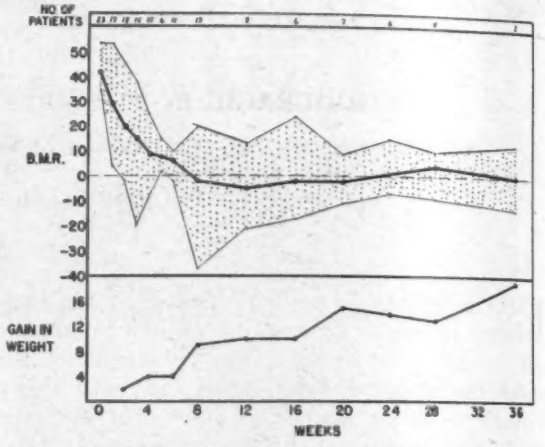

FIGURE 2. *The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 23 Patients with Moderately Severe Thyrotoxicosis.*

(basal metabolic rate, +55 to 89 per cent) than in the others. It did not become normal on the average, however, until after five weeks of treatment, whereas in the moderately severe cases (basal metabolic rate, +35 to 55 per cent) this interval was four weeks, and in the mild cases (basal metabolic rate, +15 to 35 per cent) only three weeks. The basal metabolic rate had become normal in each patient within an interval of ten days to seven weeks. This statement does not apply to all the

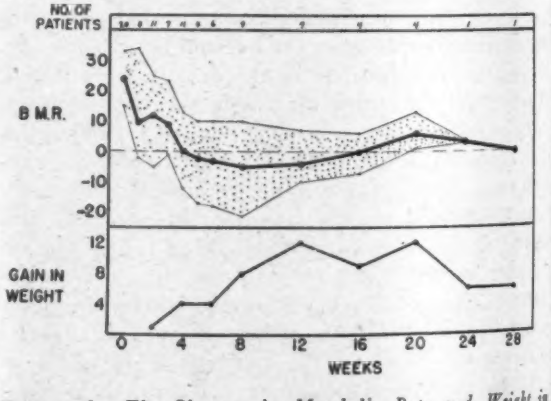

FIGURE 3. *The Changes in Metabolic Rate and Weight in Association with the Thiouracil Treatment of 20 Patients with Mild Thyrotoxicosis.*

cases subsequently operated on, because several of these patients were treated for less than two weeks. During the interval that they were observed, however, there was no difference in their response to therapy from that of the unoperated cases. In essentially all the patients the metabolic rate remained

normal following treatment, although occasionally a value slightly above normal was obtained that, on questioning the patient, was usually found to be related to excess work before the test, a respiratory infection or some other such extraneous factor. The slight tendency to a rise in the metabolism after about two months of treatment was probably related to reduction in dosage. In an attempt to use the minimal effective quantity of thiouracil the dosage was occasionally reduced to as little as 0.1 gm. daily, which was sometimes inadequate. On the other hand, when the dosage was too large, the metabolic rate became undesirably low and the patient experienced distinct clinical manifestations of hypothyroidism. However, these changes could be rapidly altered by a slight readjustment in the dosage.

In most of the patients there was little or no gain in weight during the first two weeks of treatment. Indeed, in many cases there was an actual loss in weight. Gain in weight was rapid with four to eight weeks of treatment and gradually increased thereafter, occasionally becoming excessive.

There were 13 patients who received iodide therapy either within one month before commencing thiouracil or during its administration. Consequently, these cases are discussed separately from the foregoing 59. In Figure 4 are plotted the changes in the metabolic rate of these patients, each of whom had taken potassium iodide regularly for an interval of one month to two years, this therapy having been discontinued during a period of four weeks preceding thiouracil treatment; in this group a continued iodide effect was to be expected. At the time that the thiouracil therapy was begun the metabolic rate was normal in only one case. These patients tended to be *resistant to thiouracil therapy*, particularly during the first three weeks. In fact, in 3 of 5 cases in which there was an immediate transition from iodide to thiouracil therapy, a distinctly greater elevation in the metabolic rate was found two weeks later. Whereas a normal metabolism was ultimately obtained in the 5 patients treated for eight weeks or longer, this interval was distinctly longer than that required in the 59 cases previously discussed (Figs. 1, 2 and 3). This delayed response was observed even though no iodide had been given for as long as three weeks preceding thiouracil. The course of a tenth patient was apparently similar, but the data in this case are incomplete. The remaining 3 of the 13 patients received potassium iodide and thiouracil concomitantly. The response in two of these cases was about the same as one would expect from the use of thiouracil alone, whereas in the third case the metabolic rate declined very slowly; the latter patient had taken iodide for two years before beginning thiouracil treatment.

In 2 of the 59 patients already discussed, the changes in metabolic rate when the therapy was changed from thiouracil to potassium iodide were also observed. In each case a slight exacerbation occurred.

Changes in Protein-Bound Iodine Content of Plasma

Although the accurate determination of the protein-bound iodine* content of the plasma represents one of the best methods of estimating the amount of thyroid hormone produced, the procedure involved is long and tedious and thereby tends to reduce extensive use. Nevertheless, in some cases the changes induced in this fraction by thiouracil therapy have been followed, the method of Riggs and Man[3] being used. The normal range is from 4 to 8 gammas per 100 cc. A few of the results have previously been reported.[2]

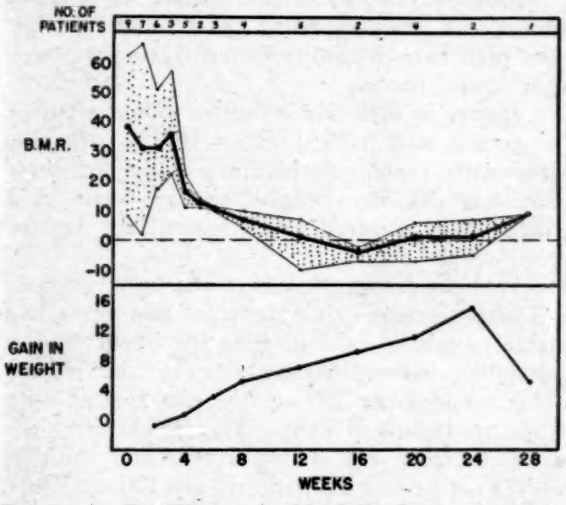

FIGURE 4. *The Changes in Metabolic Rate and Weight in Association with the Treatment of 9 Patients with Thyrotoxicosis Who Had Previously Been Given Potassium Iodide. Note that the decrease in metabolic rate, as well as the gain in weight, took place more slowly than it did in those who had previously received no iodide therapy (Figs. 1, 2 and 3).*

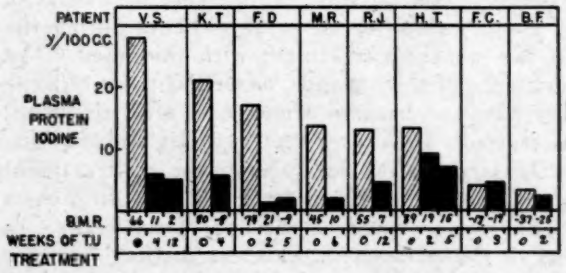

FIGURE 5. *The Changes in the Concentration of the Protein-Bound Iodine of the Plasma Compared with those in the Basal Metabolic Rate following Thiouracil Treatment.*

Patient F. C. *had a colloid goiter,* B. F. *had myxedema, and the others had thyrotoxicosis. The dosage of thiouracil was, for the most part, 1 gm. daily.*

As shown in Figure 5, the protein-bound iodine returned to normal in each of the thyrotoxic patients in whom the determination was done. Indeed,

*The protein-bound iodine is composed of the so-called "D" and "T" iodines, which are essentially equivalent, respectively, to the di-iodotyrosine and the thyroxin content of the plasma.

in 2 subjects it reached the myxedema range. The data are sufficient to show that in at least 4 cases the iodine level became normal before the metabolic rate did. If this principle held in most cases, one would expect the plasma protein iodine to be normal in the majority of patients in about four weeks or less. The level was essentially normal in 2 cases within four weeks and in 2 others within two weeks. In 2 subjects estimations were made as long as twelve weeks after beginning thiouracil treatment, and in each case the iodine concentration was well within normal limits.

No change in the plasma protein iodine occurred in a patient with colloid goiter (F. C.) who was treated with 1 gm. of thiouracil daily for three weeks; nor did any definite change occur in a myxedematous subject (B. F.) similarly treated for two weeks.

One patient who stated that she had taken 15 drops of potassium iodide daily for two years had a basal metabolic rate of +44 per cent and a thyroxinlike iodine concentration in the plasma of 11.6 gammas per 100 cc. She was treated with 0.4 gm. of thiouracil daily. Five weeks later the basal metabolism was +15 per cent and the thyroxinlike iodine was 6.9 gammas per 100 cc. Thus, whereas this patient was not well controlled with iodide, she showed a distinct improvement when thiouracil therapy was given concomitantly with the iodide, although the response was slower than is generally the case when thiouracil alone is used.

Changes in Thyroid Gland

The changes in the size and consistence of the thyroid gland are difficult to discern. Nevertheless, attempts were made to evaluate these factors at each visit of the patient. An increase in the size of the gland was observed in 11 patients during the first few weeks of treatment with thiouracil. The consistence of these glands, as well as those of some other patients, became firmer soon after thiouracil was started. In 2 cases the thyroid gland was distinctly larger after several months of treatment than it was at the beginning of therapy. In 8 cases no change was noted at the end of six weeks. In most of the patients, however, a distinct decrease in the size of the thyroid gland was observed after more than six weeks of treatment with thiouracil, and in 21 cases there was a 33 to 66 per cent decrease. In a few cases glands that were formerly two to three times normal size and of firm consistence returned to an essentially normal state. In 9 of the 72 patients desiccated thyroid was used for several weeks in doses of 0.5 to 1.5 gr. daily to reduce the size of the thyroid gland. In most of the cases such treatment proved to be of advantage.

Ocular Changes

Five patients initially exhibited changes in the orbits characteristic of those found with malignant exophthalmos.[4] In each case the manifestations became worse during the first few weeks of treatment with thiouracil, and in 1 case they became severe, the patient developing marked palpebral edema, conjunctival injection and chemosis, marked lacrimation and several corneal ulcers. Desiccated thyroid was used in the treatment of these subjects after the metabolic rate had become normal under thiouracil therapy. The rationale of this treatment will be discussed later.

All the patients who exhibited a stare and widened palpebral fissures experienced a distinct improvement in these disturbances as the metabolism became normal. Many patients stated that their eyes were "looking normal again."

Complications

The most serious complication encountered was leukopenia with agranulocytosis, which was experienced by 1 patient. This was discovered at the end of six weeks of treatment, during which the patient received 0.6 gm. of thiouracil daily for the first two weeks, 0.4 gm. daily for the next two weeks and 0.2 gm. daily for the last two weeks. A white-cell count was made when the patient complained of fever and an infected finger. She was treated with Pentnucleotide and large doses of crude liver extract. Complete recovery resulted, although only a few granulocytes were present for a period of seven days. In another case the white-cell count dropped to 3200, with 20 per cent granulocytes, only a few days after beginning thiouracil treatment. In spite of continued therapy, however, the white-cell count returned to normal and the granulocytes increased to 50 per cent. Subsequently, the patient took thiouracil for more than six months and remained in good health. Leukopenia and granulocytopenia were seen in some other cases, but the incidence was apparently no greater than that observed in untreated thyrotoxic patients.

Four patients developed a morbilliform rash, associated with itching, but this disappeared in spite of continued treatment. Three others developed moderately severe urticaria. One of these patients discontinued thiouracil for three days and then resumed it without recurrence. Another with urticaria developed painful, swollen and stiff joints lasting one week. Following this episode iodide therapy was substituted. The third patient developed urticaria and fever after eight months of thiouracil therapy and a thyroidectomy was then performed.

Six patients developed swelling of the legs that was not associated with hypoproteinemia, cardiac failure or evidence of renal damage, but data obtained[5] from some of these patients, as well as others, indicate that thiouracil in certain dosages may cause a retention of sodium, chloride and water. A decrease in the carbon dioxide combining power of the blood was also found in a few of these patients, but

these changes disappeared in spite of continued therapy.

Two patients experienced nausea and vomiting during the first week of treatment, but these symptoms disappeared without stopping of the medication. Another patient had swelling and soreness of the submaxillary salivary glands, which subsided without alteration of the treatment.

In summary, untoward reactions of some sort, ranging from mild to severe, occurred in 13 of the 72 patients treated. In only 3 were these reactions of such severity as to necessitate discontinuation of the drug, although in some cases therapy was omitted until the symptoms ceased.

Thyroidectomy following Thiouracil Treatment

A thyroidectomy was performed on 22 thyrotoxic patients and on 3 patients with colloid goiters, each of whom had received thiouracil preoperatively in amounts and for periods of time designated in Table 1. The colloid goiters were removed chiefly because of their large size, as was the case in 4 thyrotoxic cases. In 6 cases the gland was removed because the patient desired this treatment at the outset. In 11 cases it was removed because such factors as distant residence or business obligations interfered with adequate observations. The gland was removed from 1 patient after she had developed urticaria that was apparently due to thiouracil. However, *in no case was a thyroidectomy performed because of any evidence that the metabolic rate would not return to normal* with the use of thiouracil alone. In fact, in 13 of these 22 patients the basal metabolism was normal at the time of the operation. Eight of the other 9 patients had received treatment for less than four weeks, but during this interval they showed the usual lowering of the basal

Table 1. *Data in Cases With Thyroidectomy.*

Name	Thiouracil Treatment		Clinical Data during operation		Clinical Data following operation		Weight of Thyroid Gland	Dry-Weight Content of Thiouracil		Remarks
	Duration before operation	Daily dosage before operation	Maximal Pulse Rate	Maximal Blood Pressure	Maximal Pulse Rate	Maximal Temperature		Entire gland	Colloid	
	days	*gm.*		*mm.Hg.*		*°F.*	*gm.*	*mg/100 gm.*	*mg/100 gm.*	
Toxic Goiter										
H.A.	8	0.6	150	165/95	125	100.5	23	12		
J.B.	35	0.4	90	180/120	88	101	14			
B.J.	1	1.0	105	160/80	100	99.5	14	14		Preoperative treatment consisted of potassium iodide; thiouracil given on day preceding operation.
I.H.	47	0.4	130	170/100	100	101	500	22	25	Desiccated thyroid, 1 gr. daily, for first 30 days of thiouracil treatment
M.A.	37	0.4	120	165/110	96	99.8	39	5		Desiccated thyroid, 0.5 gr. daily, for first 23 days of thiouracil treatment
H.O.	90	0.6	125	200/110	100	100	29	23		
W.O.	19	0.4	90	160/70	90	102	35	39		
L.A.	26	0.6	140	220/90	140	101	76	8		Potassium iodide for 6 weeks, ending 10 days before operation
	68	0.6	110	190/110	100	100	59	14		
D.E.	30	0.3	130	145/90	105	101.5	32			
I.T.	27	0.4	150	170/110	105	100	20	9		
B.A.	12	0.6	120	150/75	110	100.5	22	15		Potassium iodide for 2 months, ending 3 weeks before beginning of thiouracil treatment
G.A.	32	0.4	100	160/100	128	100	44	18	60	
B.O.	9	0.4	145	180/70	130	101.5	50	6		Potassium iodide for 4 months, ending 2 weeks before thiouracil treatment
C.O.	19	0.4	110	170/100	120	101.5	20	8		
M.U.	22	0.4	115	105/80	95	101	9	28		Potassium iodide, as well as thiouracil, for 1½ days before operation
S.K.	23	0.4	110	140/70	95	101.5	21	20	68	Potassium iodide, as well as thiouracil, for 1 day before operation
M.C.	23	0.4	160	195/130	135	99	61	19	41	
K.O.	13	0.6	110	150/80	120	100	23	21	31	
R.O.	24	0.6	105	140/80	100	100	40	12	49	Potassium iodide, as well as thiouracil, for 14 days before operation
M.N.	5	0.6	180	185/120	128	101	14	0		Thiouracil for 5 days, beginning 17 days before operation; potassium iodide for 9 preoperative days.
T.R.	240	0	155	165/100	110	101	42	14		No thiouracil for 7 days before operation
L.O.	8	0.6	80	190/95	108	101.5	14	17		Potassium iodide for 2 months, ending 5 weeks before thiouracil treatment
Colloid Goiter										
P.O.	4	0.6	100	125/80	105	100	8	8		
M.G.	9	0.6	130	220/125	120	101	255	28		Potassium iodide 1 day before operation
G.R.	11	0.6	90	225/135	100	101	150	12		

metabolic rate that occurred in the nonoperated group. The remaining patient had a basal metabolism of +17 per cent at the time of operation, having received thiouracil for five weeks. Judging from the course of other cases, however, the rate would most likely have been normal within another week.

The actual duration of thiouracil treatment preceding operation varied from one day to two hundred and forty days, and the daily dosage was usually 0.4 or 0.6 gm. Some of the patients had iodine therapy either before, during or after the thiouracil therapy, as noted in Table 1. One patient was operated on in two stages under cyclopropane and ether anesthesia. There were no greater technical difficulties in the removal of the gland after thiouracil therapy than exist after iodide therapy, except for slightly more vascularity and friability of the tissue. The maximal pulse rate during the operation varied from 80 to 180, averaging 123. In 16 subjects it never exceeded 130. The highest systolic blood pressure varied from 135 to 220, averaging 169, and the highest diastolic pressure varied from 70 to 130, averaging 95. Of course, almost throughout the operation in each case the pulse rate and blood pressure remained at distinctly lower levels than indicated above. The maximal pulse rate following the operation varied from 88 to 140, averaging 110, and the maximal temperature ranged from 99 to 102°F., averaging 100.7°F. The postoperative period of hospitalization varied from five to fifteen days, averaging eight days. On the whole, the course of the patients during and following the operation was relatively smooth in all but 3 cases, these patients being excited and restless. In none of the latter cases had thiouracil been given for as long as ten days. In general, the patients treated with thiouracil and without iodine for as long as three or four weeks had an extremely smooth course.

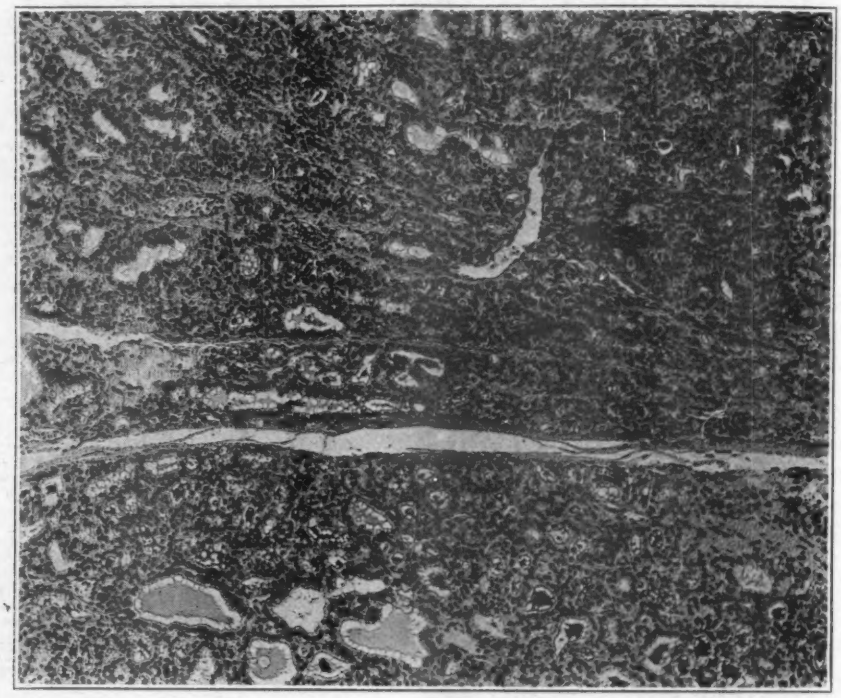

FIGURE 6. *Section of Thyroid Gland of a Thyrotoxic Patient Treated with Thiouracil for Twenty-Three Days.*

Note the scanty colloid and the great mass of cells. Most of the colloid is quite pale, although a few deep-staining clumps are seen in the right lower corner. The cells are hyperplastic, and the lumens of many acini are largely obliterated. Increased interstitial tissue is observed in some areas.

It is much too early to evaluate the results of operation, although with the short periods of observation made thus far there has been no evidence of persistence or recurrence of toxicity.

Anatomic and Chemical Changes in Thyroid Gland

Anatomic Changes

The thyroid glands of patients who received thiouracil for more than two weeks were distinctly firmer than normal, having a rubbery consistence. The cut surface was uniformly grayish-yellow, with a slightly pink hue. Many of the glands had little visible colloid and were more friable than normal. On microscopic examination a moderate variation in the structure of the gland was found. In the group of patients who received no iodide at any time but were treated with thiouracil for intervals of

eight to thirty-two days, it was found in general that the longer the drug had been given the greater the thiouracil effect (Fig. 6). Glands showing this effect to a pronounced degree possessed many or all the following characteristics. A marked scarcity of colloid was readily noted, the tissue consisting of an almost solid sheet of cells in many areas. The colloid that was present tended to be quite pale. Many acini appeared small and contracted, the lumen having almost entirely disappeared. On the other hand, a few acini had an enlarged lumen and these were apt to show papillary projections. The cells were tall and columnar. There was an increase in the interstitial tissue, with a noticeable increase in fibroblasts, lymphocytes and collagen. In some areas there were foci of dense lymphocytic infiltration ramifying between the acini in a disorderly manner, but it was commoner to observe well-circumscribed lymph follicles, many with prominent germinal centers, consisting of lymphoblasts in the center with a few clumps of collagen and an occasional macrophage, all densely surrounded by lymphocytes. These lymph follicles were usually subcapsular. They were present in about half the cases, and were larger and more prominent than the occasional cluster of lymphocytes commonly seen in the thyroid gland.

Changes were seen varying in degree from the ones described above to those of an untreated thyrotoxic gland. In no case, however, was there anything resembling the appearance of iodized glands. There was no striking difference in the appearance of the glands of the 2 patients treated for three months and eight months, respectively, from that of the glands of certain patients treated for only one month.

It was of interest to note that in a case treated with thiouracil for twenty-four days, during the last fourteen days of which potassium iodide was also given, the gland showed a classic iodine effect with no evidence of a thiouracil effect. A patient who also took thiouracil for five days, nothing for the next three days and then potassium iodide for the next nine days was found to have no definite iodine effect in the thyroid, the gland appearing like an untreated thyrotoxic gland with perhaps a slight thiouracil effect.

One patient was given iodide for six weeks, during the last nine days of which thiouracil was given. The latter drug was continued until a hemithyroidectomy was performed seventeen days later. The gland showed a large amount of moderately deep-stained colloid and slight hyperplasia of the acinar cells. Thiouracil treatment was continued, and forty-two days later a second operation was performed. The tissue removed at this operation showed less colloid but more hyperplasia than did the portion removed at the first one. It seems probable that the iodide therapy influenced the effects of thiouracil long after the former had been discontinued. Two other patients exhibited this same phenomenon to some extent.

Changes in Concentration of Thyroxin Iodine

In 11 thyrotoxic cases about two thirds of each thyroid gland was analyzed for its thyroxin iodine content by the method of Leland and Foster.[6] The results were compared with those given by Gutman, Benedict, Baxter and Palmer[7] for normal glands, iodized exophthalmic glands and noniodized exophthalmic glands. The glands of 7 patients treated with thiouracil and no iodide had distinctly less thyroxin iodine than did those of patients who received no treatment (Fig. 7). There was an extremely small amount of thyroxin iodine in the thiouracil-treated glands, as compared with the quantity in normal or iodized exophthalmic glands. Of the 4 patients who had received iodide therapy, one patient (B. A.) had a large amount of thyroxin iodine in the gland although she had had no iodide for five weeks. On the other hand, another patient (B. O.) with a similar schedule of treatment had less thyroxin iodine than the average amount in nontreated exophthalmic glands. One patient (M. U.) who had never had iodide treatment except for the day and a half preceding operation had a relatively large concentration of thyroxin iodine in her gland. The fourth subject (L. A.), who was treated with iodide for six weeks, ending ten days before hemithyroidectomy, had essentially the same concentration of thyroxin iodine as in the average untreated exophthalmic gland. Although

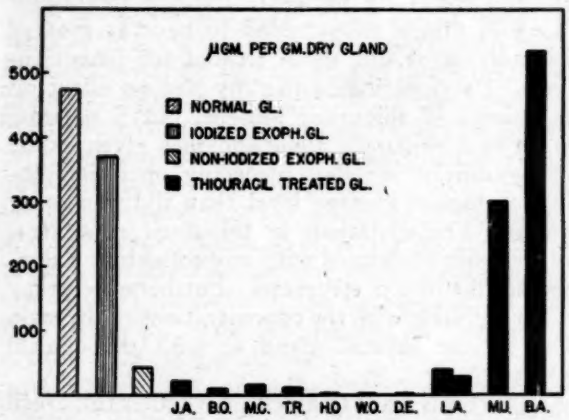

FIGURE 7. *Thyroxin Iodine in Thyroid Glands (micrograms per gram dry tissue).*

The average values for the normal glands and for the iodized exophthalmic glands were taken from Gutman and his coworkers,[7] and the average value for the noniodized exophthalmic glands was calculated by these authors from the data of Wilson and Kendall.[8] Patients B. O., L. A., and B. A. had had some iodide therapy before thiouracil treatment was begun. The results of a two-stage operation are given for patient L. A. Patient M. U. had no iodide until a day and a half before thyroidectomy, a relatively high concentration of thyroxin iodine was present. Note especially the small concentration of thyroxin iodine in the glands of patients treated with thiouracil and no iodide.

after forty-two days of additional thiouracil treatment the amount of iodine in the second half of the gland had decreased, it was still larger than that found in the glands of patients who had received thiouracil and no iodide.

Concentration of Thiouracil

Immediately after removal of the thyroid gland an analysis was begun to determine the concentration of thiouracil therein, using the method of Williams, Jandorf and Kay.[9] In the patients who had continued thiouracil therapy until the day of operation, the values ranged from 5 to 39 mg. per 100 gm. of dried gland. A patient (T. R.) who had had no treatment for seven days preoperatively was found to have 14 mg. per cent. Patients treated for as long as fifteen days tended to have as great a concentration as did those treated for longer intervals. Previous iodide therapy had no effect on the amount of thiouracil present, but 3 patients treated with thiouracil alone and then given iodide therapy during the day preceding operation obtained a higher average level than did the other patients. The variations in thiouracil concentration were not associated with any consistent alterations in histologic structure. Furthermore, they did not correlate with the concentrations of thyroxin iodine in the thyroid gland or with the clinical response.

An effort was made to ascertain whether thiouracil was stored equally in the colloid and in the parenchyma. In 6 cases, a portion of the gland was sectioned into several large pieces and these were gently squeezed by a metal compressor. By this procedure, which is admittedly crude, it was hoped to express some colloid and not many cells or tissue fluid. The fluid so obtained in the 6 cases contained a concentration of thiouracil distinctly greater than that of the whole gland, when expressed in terms of dry weight (Table 1). Two glands were given a second and a much firmer compression with the hope of obtaining a moderate amount of tissue fluid. This fluid and the residual tissue were separately analyzed for the concentration of thiouracil. The tissue fluid had a higher concentration of thiouracil than did the residual tissue (Table 2). When the quantity of thiouracil was expressed in terms of wet weight there was only a slightly greater concentration in the colloid than was present in the gland as a whole.

TABLE 2. *Distribution of Thiouracil in the Thyroid Gland.*

NAME	SPECIMEN	CONTENT OF WATER	CONTENT OF THIOURACIL	
			DRY WEIGHT	WET WEIGHT
		%	*mg./100 gm.*	*mg./100 gm.*
M.C.	Whole gland	80	19	4
	Colloid	88	41	5
	Tissue fluid	86	39	5
	Residue	77	18	4
K.O.	Whole gland	77	21	5
	Colloid	80	31	6
	Tissue fluid	76	16	4
	Residue	74	12	3

The problem of the distribution of thiouracil between colloid and cells was also approached by comparing its concentration in glands containing little colloid with that in those containing moderate amounts. No significant differences were found.

DISCUSSION

The experiences reported here in the treatment of thyrotoxicosis with thiouracil indicate that this drug can be depended on in essentially all cases to lower the basal metabolic rate to a normal range and to maintain it at that level so long as treatment is continued. Associated with this response in the basal metabolic rate is a clinical remission of the disease, with disappearance of tachycardia, hyperidrosis, nervousness, diarrhea, weight loss and other toxic manifestations.

Thiouracil causes a decrease in the protein-bound iodine of the blood and in the thyroxin iodine of the thyroid gland, but does not inhibit the hypermetabolic effects of preformed thyroxin.[2] These facts indicate that thiouracil inhibits the production of the thyroid hormone, but the exact process by which this is accomplished has not yet been determined. Presumably, when the production of the thyroid hormone is markedly inhibited, there results an excessive production of thyrotropic hormone, which in turn causes hyperplasia of the acinar cells of the thyroid and certain manifestations of malignant exophthalmos.[4] Thus, as we have observed in several cases, with the use of thiouracil in excessive quantities in thyrotoxic patients a still greater enlargement of the thyroid gland may result and the manifestations of malignant exophthalmos may be accentuated. Under such circumstances it is advisable to reduce the dosage of thiouracil. In some cases, however, the use of desiccated thyroid also seems indicated, since it not only inhibits the production of thyrotropic hormone but also exerts a diuretic effect that is of advantage in the control of the severe cases of malignant exophthalmos. To be sure, on theoretical grounds one may argue that the same thing can be accomplished by permitting the patient's own thyroid gland to manufacture more hormone. Nevertheless, we have thus far had better success by decreasing the thiouracil to a sufficiently small dosage to maintain a normal metabolic rate and then giving 1 to 1.5 gr. of desiccated thyroid daily. Before adopting this policy, however, we first sought to discover whether thiouracil would inhibit the inactivation of administered thyroid, it having been shown[10] that persons with normal thyroid glands can inactivate large quantities of desiccated thyroid or thyroxin.

To elucidate this problem 3 patients were treated with relatively large doses of desiccated thyroid for intervals of thirty to fifty days, during the last two or three weeks of which 0.6 gm. of thiouracil was administered daily. No significant changes in the basal metabolic rate occurred in any of these pa-

tients (Fig. 8). Furthermore, the thyroxinlike iodine of the plasma, determined in 1 case (D. U.) actually decreased following the thiouracil treatment.

Clinical studies were also conducted that indicated that thiouracil can inhibit the effect of relatively large amounts of thyrotropic hormone in increasing the production of thyroid hormone. Williams and Bissell[2] found that when 1 gm. of

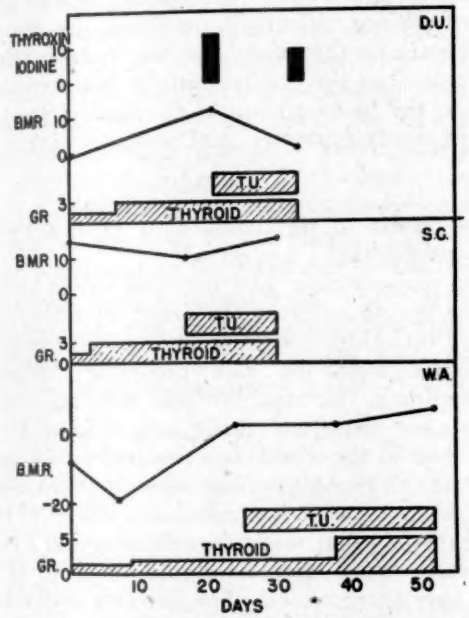

FIGURE 8. *Basal Metabolic Rates in 3 Patients without Thyroid Disease Treated Simultaneously with Thiouracil and Desiccated Thyroid.*

Note that no significant change in the basal metabolic rate resulted from large doses of desiccated thyroid whether or not thiouracil (0.6 gm. daily) was also given. A slight decrease in the thyroxin iodine (expressed in micrograms per 100 cc.) of the plasma resulted in one case (Patient D. U.).

thiouracil was given daily with 2 cc. of thyrotropic hormone (Antuitrin T) in sesame oil to a normal subject for a period of ten days, no elevation in the basal metabolism resulted, although a goitrogenic effect was noted. Subsequent unpublished studies showed that no change results in the concentration of the protein-bound iodine of the plasma. This experiment was repeated in another normal subject using the same amount of thyrotropic hormone for eight days but no thiouracil. Although no significant elevation in the metabolic rate occurred, the plasma iodine showed a marked rise, increasing from 8 to 15 gammas per 100 cc. Thus, the marked inhibitory effect of thiouracil in the first case is apparent.

In choosing the ideal dosage of thiouracil it is desirable to use the smallest amount necessary to obtain a remission of the disease, but it has been found that this quantity varies with different patients. In an attempt to establish an objective method of ascertaining this dosage, Williams, Kay and Jandorf[11] determined in a large number of cases the concentration of thiouracil in the blood when the patient was given from 0.2 to 1.2 gm. daily. The blood level remained relatively constant, regardless of what dose was given. Furthermore, using the above range of doses we have found no directly proportional concentration of the drug in the thyroid gland. In the course of varying the dosage, however, the amount of drug necessary to obtain an adequate response in thyrotoxicity was distinctly less than the amount that was first used.[1, 2] An outline of treatment with thiouracil that we have found extremely satisfactory is the following: 0.2 gm. three times daily for the first two weeks, followed by 0.2 gm. twice daily until the metabolism is normal and then 0.1 gm. twice daily until the basal rate has been maintained well within normal limits for several weeks, when the dosage can be reduced to 0.1 gm. daily. Cases have rarely been encountered in which larger doses were necessary, and in a number of cases smaller ones were used. Whatever schedule of dosage is to be used, it should be borne in mind that thiouracil is rapidly absorbed and excreted.[11] Thus, it is better to give two or three decreased doses per day than it is to give only one. On the other hand, the prescription of many small doses may cause the patient to become quite irregular in taking treatment.

Williams, Kay and Jandorf[11] found that the routine estimation of the thiouracil content of the blood and urine was of no definite aid in treatment. Most of the tissues of the body can break down large amounts of thiouracil, thereby interfering with its accumulation in the blood of normal subjects as well as of patients with severe disease of the heart, kidneys or liver.

Of the various complications thus far encountered, the only one to cause appreciable concern is agranulocytosis. Patients who develop urticaria or any other allergic manifestation, however, should be carefully observed when treatment is resumed, since other sensitivity phenomena may result.

Much more must be learned before the role of thiouracil in the medical treatment of thyrotoxicosis can be fully evaluated. In most cases its great dependability in controlling the toxicity makes hospitalization unnecessary. Furthermore, the majority of patients can continue regularly with their work. Nevertheless, patients treated in this manner should maintain close contact with the physician, particularly during the first two months. How many patients can discontinue therapy without a relapse in the disease remains to be demonstrated. The prolonged course of treatment does not of itself constitute much of a burden, since the maintenance dosage does not have to be varied much once it has been properly estimated. The possibility of chronic complications and the development of therapeutic unresponsiveness to the drug must be borne in mind, although we have thus far seen no evidence of either.

By accurately regulating the dosage of thiouracil it is believed that the goitrogenic effect can be kept low. In fact, in most cases the gland tends to decrease in size. Two reasons for this decrease may be advanced: a marked decrease in the content of colloid, permitting a collapse of the acini, and an exhaustive phenomenon — an atrophy of the cells resulting from the prolonged stimulation by the thyrotropic hormone. The first phenomenon was often observed in our patients, but no evidence of the second has yet appeared.

In spite of the fact that many thyroid glands have decreased in size with treatment, it is not considered advisable to give prolonged thiouracil treatment to a patient who has an extremely large gland, since there is some possibility that the gland will actually become larger. Since some of these patients have compression of the surrounding structures, the risk of further trouble should not be taken. However, the drug has been used preoperatively in some patients with extremely large glands. In fact, the gland of one patient weighed 500 gm. at operation in spite of a decrease in the neck circumference of 2.5 cm. during treatment. In this case, as in somewhat similar ones, desiccated thyroid was used with the thiouracil.

Thus far, we have not found that iodide used preceding or during thiouracil treatment is of any advantage. In fact, the patients who had iodide previously responded more slowly to thiouracil than did those who had not had any. Furthermore, in some cases there was actually an exacerbation of the disease if thiouracil was suddenly exchanged for iodide. This is to be expected when one considers that iodide causes storage of the hormone in the thyroid gland, whereas thiouracil apparently does not possess this action and thereby permits escape of the stored hormone into the blood stream. Bearing these phenomena in mind, when our patients are changed from iodide to thiouracil therapy, the treatments are overlapped for about two weeks, the amount of iodide therapy during this interval being progressively decreased.

There is evidence from studies in guinea pigs that the simultaneous administration of potassium iodide and thiouracil causes a greater concentration of the latter in the thyroid gland than occurs when the iodide is omitted.[12] On the other hand, in rats after thiouracil has been given for several days the uptake of radioactive iodine in the thyroid gland is decreased.[13] Nevertheless, in a patient who was treated with thiouracil for three weeks and given iodide for 1.5 days preoperatively, a distinctly greater quantity of thyroxin iodine was found in the thyroid gland than in cases treated similarly with thiouracil without iodide.

The use of thiouracil in preoperative preparation has the advantage over iodine of dependability in causing a disappearance of the toxic manifestations of the disease in essentially every case, provided that the treatment is continued for several weeks. Because of this dependability the patient may be permitted, in most cases, to perform a part or all of his usual activities during the period of preparation for the operation. Of course, during this interval adequate rest and a high-caloric diet supplemented by moderate amounts of vitamins, particularly thiamine and the members of the vitamin B complex, are desirable. A period of preparation of four to five weeks has thus far proved satisfactory. Since thiouracil decreases the quantity of thyroxin in the thyroid gland, in cases treated with this drug there is potentially less thyroxin to get into the blood stream at the time of operation than in the cases treated with potassium iodide.

Summary

The results of treatment with thiouracil of 72 thyrotoxic patients are given.

The subjects who had not had iodide therapy for one month or more (59 cases) were arbitrarily divided into three classes according to the height of the basal metabolic rate preceding treatment. The decline in the basal rate was more rapid in the severe cases (basal metabolic rate, +55 to 89 per cent) than in the others, but required an average of five weeks to become normal, whereas in the moderately severe cases (basal metabolic rate, +35 to 55 per cent) only four weeks was necessary, and in the mild ones (basal metabolic rate, +15 to 35 per cent) only three weeks. The lowering of the basal metabolic rate in patients who had taken iodide until the thiouracil treatment was started was slower. All patients, however, regardless of the type of thyrotoxicity or of previous treatment, eventually attained a normal metabolic rate and a remission of the disorder.

Thirty-five patients were treated with thiouracil for more than four months and 16 for more than six months. Essentially all patients maintained a normal basal metabolism. In 4 patients who discontinued therapy after a few months, a relapse occurred in about three weeks, but a remission was again obtained with thiouracil treatment.

In the few cases where the plasma protein iodine content was determined this value became normal and tended to do so before the metabolic rate became normal. Although a transient increase in the size of the thyroid gland occurred in several cases, in the majority an ultimate decrease in the size of the gland resulted, this change being marked in some subjects. A few patients with malignant exophthalmos experienced an exacerbation in this process under thiouracil therapy, but with a decrease in the dosage of thiouracil and the use of desiccated thyroid an improvement resulted.

One patient developed agranulocytosis; other complications consisted of morbilliform rash, urticaria, allergic arthritis, edema of the legs, vomiting and enlargement of the submaxillary salivary glands.

Although many estimations were made of the content of thiouracil in the blood and urine, these determinations are not necessary, since with the range of dosage employed the drug has not been found to accumulate appreciably in the blood, in spite of the presence of severe disease of the kidneys and liver.

For reasons other than an unsatisfactory response in the toxic manifestations of the disease 22 patients were subjected to thyroidectomy. The operative and postoperative course was relatively smooth, particularly in the patients treated with thiouracil for three weeks or longer preceding operation. A chemical analysis of these glands for the concentration of thiouracil showed a great variation in the amount of drug present. With these cases there was no correlation of the therapeutic response with the level of the drug in the gland. The thyroxin iodine was found to be extremely low in most of the glands that were analyzed. The pathologic alterations in the thyroid gland resulting from thiouracil treatment are described; they are quite unlike the changes found after iodide therapy.

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FAVUS IN MASSACHUSETTS*

A Report of Two Cases

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FAVUS is a rare fungus infection, and only a few cases of it have been reported from Massachusetts. Search of the records of the Boston City Hospital revealed that no cases had been seen there during the last ten years. This report of 2 cases is of interest, first because of the rarity of the disease, and second because of the satisfactory response to therapy.

The disease is usually caused by *Achorion schönleinii*, but on rare occasions *A. quinckeanum* has proved to be the etiologic agent. The fungus may be found in or on the hairs, in the scutula and in and on the skin and nails. Microscopically the hairs, when softened in 30 per cent potassium hydroxide solution, show a characteristic diagnostic picture. They are usually covered with air bubbles, which are thought to be the result of displacement of air in the dead fungic filaments by the potassium hydroxide solution. On the outside, both spores and filamentous forms occur; within the hairs, coarse mycelial threads, usually broken into oblong bars and into chains of spores (arthrospores), are found running parallel to the long axis of the hairs. These intrapilar filaments and spores are coarser and fewer than are those seen in Trichophyton infections, and favus spores are two to three times larger than are the spores seen in Microsporon infections (Fig. 1).

The scutula, which may be found on the scalp or glabrous skin, comprise almost pure cultures of the organism. Achorion is the only pathogenic fungus that grows on the skin in such pure form.[1]

On Sabouraud's medium, the organism grows slowly to form a discoid, smooth, waxy or semitranslucent, convoluted, yellowish-brown colony that frequently grows deeply into the medium, causing large fissures to occur in it. Microscopically the culture shows coarse, septate and branched filaments with numerous chlamydospores, arthrospores, terminal clubs and favic "chandeliers" (Fig. 2).

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Case Reports

Case 1. E. S., an 18-year-old girl of Jewish parentage, was first seen at the Out-Patient Department of the Boston City Hospital in August, 1941, complaining of a rash on the scalp of 2 years' duration. This had started as a small spot of baldness and had enlarged despite various local applica-

tions prescribed by several physicians. The parents were born in Lithuania and had come to America 9 years prior to the birth of the patient. The latter was born in Pennsylvania and had lived there during the first 14 years of life, after which the family moved to Massachusetts.

Physical examination revealed an irregularly rounded area of patchy alopecia approximately 10 cm. in diameter over the vertex of the scalp. Many of the hairs in this area were

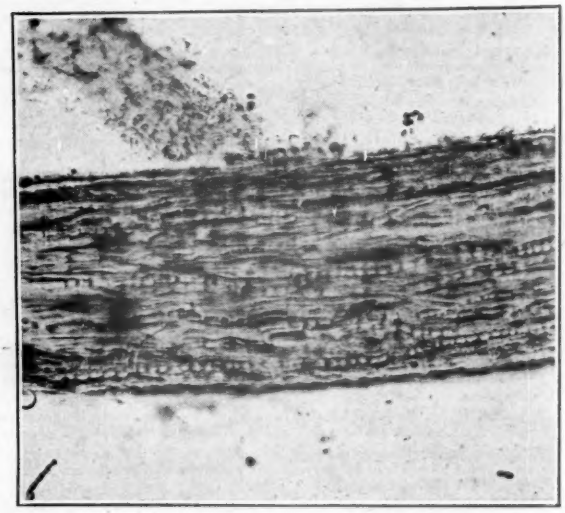

FIGURE 1. *Hair in Potassium Hydroxide Solution, Showing Chains of Spores within the Hair.*

dull and bent at acute angles, and some were broken off about 2 cm. from the scalp. There were several sulfur-yellow scutula, each pierced by a hair, adhering to the skin, which showed areas of atrophy and scarring. Examination of the scalp under a Wood's filter* revealed the yellowish-green fluorescence that is characteristic of hairs infected with Achorion.

Microscopic examination of hairs softened with potassium hydroxide solution revealed the characteristic picture of favus, and subsequent culture showed the presence of *A. schönleinii.*

Examination of the other members of the family revealed no evidence of active or healed infection with Achorion.

CASE 2. J. C., a 17-year-old girl of Italian parentage, entered the Out-Patient Department of the Boston City Hospital in July, 1942, complaining of a "rash" of the scalp of 4 years' duration, which had steadily progressed despite numerous forms of local therapy. The patient was born in Massachusetts and had never been outside the Commonwealth. Her father and mother had migrated from Italy 7 years prior to her birth.

Physical examination revealed three irregularly rounded areas of patchy alopecia involving almost the entire vertex of the scalp. The hairs of these areas were lusterless, thickened and fragile. Many were broken off close to the skin, which was studded with sulfur-yellow scutula and crusts. There were areas of scarring and atrophy of the underlying epidermis. The left leg, close to the knee, showed a single rounded, sulfur-yellow scutulum, 8 mm. in diameter, adhering to the skin.

The infected hairs showed the characteristic greenish-yellow fluorescence under the Wood's filter. *A. schönleinii* was cultured from the scalp and from the scutulum on the leg.

Examination of the other members of the family revealed no evidence of active or healed infection with Achorion.

*The Wood's filter is obtained by passing ordinary ultraviolet light from a mercury-vapor or carbon-arc lamp through glass that is so constructed that it absorbs all visible light (wave lengths 0.4100 to 0.7600 microns) but passes wave lengths between 0.3100 and 0.4100 microns. The best glass for dermatologic use is one whose maximum transmission lies between 0.3600 and 0.3700 microns. Such a piece of glass, suitably cut, may be fitted into a light-impervious cloth hood, which is placed over the source of the ultraviolet light. Examination is carried out in a dark room. Such a filter permits easy identification of hairs infected with fungi.

Therapy of favus of the scalp is notoriously difficult. Sutton and Sutton[2] state that x-ray therapy constitutes the most reliable and efficient remedy, and Ormsby and Montgomery[3] assert that such therapy offers the best method of treatment, without which months and years are consumed in effecting relief. Despite the opinion of these and other authorities, x-ray epilation is not a universally successful method of treatment; for Muskatblit[4] treated 3 cases of favus in this manner, with recurrence of the infection in all of them. A fourth case was treated with thallium by mouth. Successful epilation of the hairs followed this medication, but recurrence of the favus also occurred in this case. Muskatblit states that in his experience recurrence is common after such epilatory procedures.

Similar failure of roentgen-ray epilation to cure a patient previously under my care led to an extensive search for other more effective methods of therapy.

Trained mycologists are aware that cultures of various fungi may be killed by applying a few drops of formalin to the cotton stoppers of the tubes. The formalin decolorizes the fungi, so that the killed culture loses the characteristic and often diagnostic pigmentation of the living organisms and, incidentally, makes it valueless for teaching purposes. Such a solution, however, cannot be safely applied to the skin, for the aldehydes are well-known skin sensitizers and irritants.[5] I found that a solution of 10 per cent thymol in chloroform would kill but

FIGURE 2. *Stained Culture of* Achorion schönleinii, *Showing Segmented Filaments, Terminal Clubs and Favic "Chandeliers."*

not decolorize cultures of fungi. Since thymol does not sensitize and irritate the skin as does formalin, it was used as a therapeutic agent in these cases, being applied twice daily to the affected parts.

The patients were advised to shampoo the scalp twice weekly, and for the first three months used

the above prescription exclusively. They were instructed to epilate the hairs manually from the affected parts, and once weekly this procedure was supplemented by manual epilation under a Wood's filter at the clinic. Progress was satisfactory from the first, the patients experiencing less irritation and less scaling within two weeks of starting therapy. At the end of the third month, when it was thought that an irritant might stimulate the tissues to the formation of antibodies, it was decided to alternate the thymol with 4 per cent chrysarobin in chloroform, chrysarobin being an effective irritant and antiparasitic.

Therapy was continued for a year in each case, at the end of which time regrowth of hair was permitted. The thymol solution was applied twice weekly during the period of regrowth. Repeated examinations under a Wood's filter have failed to reveal any fluorescence. Microscopic examinations and cultures have failed to reveal the presence of the fungus over a period of one year in Case 1 and a period of three months in Case 2. Regrowth of normal hair has occurred in many parts of the previously affected areas.

Summary

Two cases of favus are reported that had apparently been acquired in Massachusetts.

The microscopic and cultural characteristics of the Achorion responsible for the disease are outlined.

A method of therapy that proved successful is described.

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MEDICAL PROGRESS

ENDOSCOPY (Concluded)*

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Esophagoscopy

Surgery. In an editorial on Russian surgeons and Russian surgery,[38] it is reported that surgery is done on a vast scale in Russia. It is stated that Yudin performed in one morning three operations of replacement of esophageal stricture by jejunum. This is certainly an amazing feat.

Carcinoma. Carcinoma of the esophagus is said to be seventh in frequency in types of carcinoma among males. Operative treatment is the only method of cure. With improved technic any segment of the esophagus can now be successfully removed surgically. As pointed out in the last year's report,[1] Wookey[39] has discussed a technic for removing the hypopharynx and upper esophagus. Early diagnosis is the most important factor in obtaining cure. All patients with difficulty in swallowing should have early x-ray examination and esophagoscopy with biopsy to establish a positive diagnosis.

Smithers, Clarkson and Strong[40] report in detail 54 cases of carcinoma of the esophagus in which roentgenologic therapy was given. Strikingly favorable responses were noted in many cases, and most of the patients showed improvement.

Pohle and Benson[41] also report on the results of radiation therapy in 85 cases of cancer of the esophagus. There were no cures. One patient, however, with cancer at the upper end of the esophagus treated by roentgenologic irradiation alone was alive and well for more than four years, and another treated by roentgenologic irradiation and implantation of radon seeds was alive and well for more than seven years. In both cases the diagnosis was confirmed histopathologically.

Benign tumor. Adams[42] reports an interesting case of fibroma of the esophagus in a forty-one-year-old woman who complained of difficulty in swallowing of seven years' duration. After a preliminary x-ray examination and esophagoscopy, a gastrostomy was performed and a tumor measuring 5 by 7 cm. was removed by the transthoracic route. Compared with cancer, dysphagia is much slower to appear.

Pain. Moersch and Miller[43] point out that esophageal pain may occur in a variety of esophageal disturbances. It varies in character, intensity and distribution. It is influenced by many extraneous factors and may closely mimic the symptoms produced by other types of serious organic disease. One of the greatest obstacles in the clear understanding of the problem of esophageal pain is the lack of exact knowledge concerning innervation of the esophagus.

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Peptic ulcer. Allison, Johnstone and Royce[44] report 10 cases of simple peptic ulcer of the lower end of the esophagus. All the patients complained of dysphagia, and in each case the cause was found to be cicatricial stenosis of the esophagus and simple ulceration, the latter being associated with chronic esophagitis and chronic gastritis. In each case the narrowing of the esophagus was associated with shortening so that a part of the stomach was pulled up into the mediastinum. The suggestion is made that this deformity, usually referred to as "congenitally short esophagus," may be acquired as the result of ulceration and scarring.

Cleaver[45] reports 10 cases of peptic ulcer of the esophagus, with pain, hematemesis and dysphagia. The pain was usually in the region of the epigastrium and at times radiated forward and around to the back. Rapid, fatal hemorrhage owing to erosion of the aorta rarely recurred; bleeding was usually much less severe. Dysphagia was mild or severe, and swallowing finally became impossible. Two complications were usually seen: perforation of the ulcer into the pleura, pericardium or bronchus and acute mediastinitis due to spread of infection from the ulcer into the surrounding tissues. The diagnosis was generally based on the symptoms and x-ray findings on swallowing barium. Esophagoscopy, although not mentioned in the summary, is considered indispensable in the differential diagnosis.

Scleroderma. Lindsay, Templeton and Rothman[46] have collected 16 cases of diffuse scleroderma, in all of which there was difficulty in swallowing. They had 5 patients of their own, only one of whom had any complaints referable to swallowing. In the other four the symptoms were clearly brought out in questioning, but the comparative severity of the pain and discomfort from the cutaneous lesions caused the difficulty in swallowing to be overlooked. In 3 of the 5 cases difficulty was experienced in introducing the esophagoscope under local anesthesia. This difficulty appeared to be due in part to inability to open the mouth more than about half the normal width or to extend the tongue beyond the mucous-membrane margin of the lower lip and tightness of the skin over the jaws and neck. In addition, none of the patients were able to produce relaxation of the cricopharyngeus sphincter by swallowing. Under general anesthesia, however, the sphincter relaxed easily and the walls in that region appeared grossly normal. Some form of general anesthesia appears to be indicated for esophagoscopy in cases of this type. In all cases, the wall of the esophagus from the beginning of the middle third downward was diffusely reddened and apparently thickened, with a lessened tendency to form normal folds. In the lower third there was a diffuse layer of white exudate, that could be easily separated off, leaving a granulating base.

In summary, these authors report that the disturbances of the esophagus are characterized by loss of peristalsis in the lower two thirds, with relaxation and mild dilatation of the lower two thirds down to the phrenic ampulla and probably some atony of the cardiac sphincter as a direct result of the sclerodermatic process; difficulty in swallowing solids or liquids, especially when in the lying position, owing to delayed emptying of the esophagus; burning pain behind the sternum about an hour after meals, which is worse on lying down and particularly on lying on the left side, probably owing to regurgitation of gastric contents into the esophagus and resulting chronic esophagitis; chronic ulceration in the lower third of the esophagus, localized chiefly in the region just above the phrenic ampulla, and probably a direct result of the esophagitis, with sclerodermatic changes as a predisposing factor; and stricture formation in the later stages, limited to the region immediately above the phrenic ampulla of the esophagus. Biopsies revealed changes in the submucosa that suggested sclerodermatic change.

Esophagitis. Paul[47] has studied the roentgenologic aspects of acute and chronic esophagitis. He believes that the acute ulcerative type is most frequently associated with peptic ulcer or develops immediately following upper-abdominal operations. Anything that tends to cause relaxation of the cardia, permitting acid gastric juice to come in contact with the esophageal mucosa, may predispose to its development. Frequent vomiting is an important factor. The use of a negative-suction apparatus in itself is of questionable value but may play a part when additional causes are present. The x-ray appearances, according to Paul, consist of a severe spasm of the distal part of the esophagus, loss of mucosal folds and a fine roughening of surfaces. The lesion tends to progress to a fibrous stricture. Chronic esophagitis of sufficient severity to be the cause of symptoms is uncommon. If it is present for a sufficient length of time, the x-ray findings may be those of a diffuse fibrous stricture, since the esophagus when involved by infection shows a great tendency toward the development of fibrosis. In other cases of chronic esophagitis the most striking x-ray manifestation is intermittent, diffuse spasm of the lower half or third, with thickening of the mucosal folds.

Foreign body. Weaver[48] reports an interesting case in which a chicken bone remained in the esophagus for fifty-six days without perforation. This case is remarkable in view of the fact that bones are especially liable to cause esophageal perforation. The patient was a man of thirty-nine who complained of constant dull pain in the region of the epigastrium, which became worse in swallowing. The bone was removed without difficulty by esophagoscopy under local anesthesia. The postoperative course was uneventful.

Nervous disorders. Hurst[49] believes that hysterical dysphagia is rare. When it does occur, the patient

has had an incident that drew his attention to the normally automatic act of swallowing. Dysphagia may occur in various organic nervous diseases as a result of paralysis of the muscles concerned in the first and second stages of swallowing. Motor neuron disease, which includes progressive muscular atrophy and amyotrophic lateral sclerosis, may be accompanied by dysphagia if the vagal nucleus is involved in the last stages of the common form that begins in the muscles of the hands. It occurs in progressive bulbar palsy and in myasthenia gravis. Hurst believes that the most frequent nervous disorder of swallowing is achalasia, commonly known in America as cardiospasm. In the treatment of this condition he keeps mercury bougies in the esophagus for fifteen minutes just before each meal for two weeks, after which the frequency of the instrumentation is gradually decreased. The patient himself passes the bougie.

Vines and Olsen[50] report a case of cardiospasm with associated pellagra. They discuss the possible role of vitamin deficiency in cardiospasm, but in their experience favorable results were not obtained by giving vitamin B_1 to 2 patients with esophageal obstruction. When obstruction at the cardia is relieved and the patient is maintained on a normal diet, caloric deficiencies and vitamins take care of themselves.

Hiatus hernia. Vinson[51] calls attention to dysphagia from hiatus hernia. In patients with the short esophageal type of diaphragmatic hernia, dysphagia results from spasm or stricture at the junction of the esophagus and the hernial sac. In those with hernia of the paraesophageal type, it results from stricture in the lower portion of the esophagus, spasm at the cardia or pressure from the herniated portion of the stomach on the lower part of the esophagus.

Extrinsic pressure as a cause of dysphagia. Tinney, Schmidt and Smith[52] report a case of mitral stenosis in which the onset of the illness and the clinical course were dominated by difficulty in swallowing. This symptom became so severe that for nine days prior to the patient's admission to the clinic she was unable to take solid foods and was able to swallow liquids only with difficulty. On roentgenoscopic examination of the esophagus filled with barium, there was no evidence of an intrinsic lesion, but the lower third of the esophagus was displaced posteriorly and compressed by a hugely dilated left auricle. The patient received only partial relief from the dysphagia following treatment of the congestive failure.

Esophagobronchial fistula. Clerf, Cooley and O'Keefe[53] call attention to the four main groups of fistulas,—congenital, neoplastic, infectious and traumatic, the first two being by far the most frequent. They report 2 cases in which esophagobronchial fistula existed for nine and thirty-two months, respectively. No definite cause could be demonstrated, although one patient had a pulmonary abscess and coughed up a mass of necrotic tissue immediately preceding the development of symptoms. There was no apparent tendency for the fistula to close after the esophagus was placed at rest. Prompt closure of the esophageal end of the fistula resulted following the esophagoscopic application of a sodium hydroxide crystal fused on a curved metal applicator and carried into the fistula for a distance of several centimeters. Both patients had subsequently been free from symptoms for more than eighteen months.

According to Haight and Towsley,[54] the surgically ideal plan for the correction of congenital atresia of the esophagus with tracheoesophageal fistula is a reconstruction of the continuity of the esophagus by an extrapleural ligation of the fistula and an end-to-end anastomosis of the esophageal segments. The first successful case of reconstruction of the esophagus by this plan is presented. The factors pertaining to operative correction of the anomaly and experiences in a series of 15 cases are discussed.

Gastroscopy

Normal stomach. Fitzgibbon[55] studied 40 healthy volunteers and found that 38 had mucosa within normal limits. Pigment spots and mucosal hemorrhages were not found and traumatic areas were insignificant, as contrasted with the tendency to bleed on slight trauma in gastric cases.

Technic. Moersch[56] has found that portions of the stomach that otherwise might not be adequately visualized by means of the gastroscope can often be brought into view by palpation. This method is of particular value in dealing with the antral portion of the stomach, and especially in examination of a stomach on which operation has been performed. The method is simple and causes the patient no distress. It is also of value in that it enables the examiner to determine the flexibility of the gastric mucosa. The information thus gained may be of assistance in distinguishing between a carcinomatous and an inflammatory type of infiltration.

Evaluation of gastroscopy. In a discussion on the use of the gastroscope as a supplementary aid to x-ray examination, Cohn and Levitin[57] point out that there are limitations to the x-ray diagnosis of gastric lesions that are not usually appreciated. Gastroscopy is of great assistance in clarifying certain doubtful roentgenologic findings and in differentiating others. It brings into direct vision lesions that cannot be demonstrated by x-ray. Benign ulcers have a gastroscopic appearance different from that of malignant ulcers. Carcinoma can be diagnosed and classified and the extent of involvement determined before surgery, information thus being obtained regarding its operability and prognosis. The course of a benign ulcer can be followed as regards its healing. Polyps that are

rarely diagnosed by x-ray can be visualized by gastroscopy and their extent determined. Malignant tumors of the stomach can be differentiated from intragastric and extragastric lesions. The hypertrophic and atrophic types of gastritis can be diagnosed only by gastroscopy. Following operation, lesions such as marginal ulcers and gastritis are ordinarily diagnosed only with difficulty. The gastroscopist can diagnose both these conditions and differentiate the distorted folds of the postoperative stomach from an ulcer. The authors conclude that gastroscopy is a simple, safe procedure and is a valuable supplement to x-ray examination.

Balfour,[58] in discussing the annual report of the Mayo Clinic on surgery of the stomach and duodenum, states that gastroscopy has not only been a distinct aid in early diagnosis of cancer but has also furnished valuable information on the significance of gastritis in relation to the development of carcinoma. One may expect that the continued use of this procedure will result in a better knowledge of the factors that predispose to cancer of the stomach.

Howard[59] discusses gastroscopy and the use of the gastroscope in the military services, stating that in the diagnosis and treatment of gastric ulcers the gastroscope is of course helpful. He also states that American physicians agree that gastritis is best diagnosed by inspection of the mucosa through the gastroscope. Tumors and ulcerations, some of which escape detection by roentgen rays, are readily visualized. The easy detection of gross gastric lesions establishes the gastroscope in its merited place in the military services and does much to promote its use in civil work.

Paulson[60] reaches similar conclusions regarding the present position of gastroscopic diseases, concluding that gastroscopy is complementary to roentgen-ray examination for diagnosis. When the roentgenograms are negative and yet suspicion of abnormality persists, gastroscopy may reveal an occasional neoplasm, erosions, peptic ulceration or gastritis. These lesions may also account for otherwise unexplained hemorrhage and a duodenal-ulcer syndrome not due to duodenal ulcer. When roentgenograms are positive, gastroscopy makes possible confirmation; a nicer differentiation grossly between benign and malignant lesions; a clearer delineation of the site and extent of the lesion, which helps to determine the question of operability; the differentiation grossly of spasm and edema from the lesion itself; and the occasional detection of an associated gastritis that may account for atypical symptoms, often erroneously ascribed to a defect of the roentgenogram in the duodenal cap but due to a healed, scarred ulceration.

Gill[61] in an analysis of 1000 gastroscopic examinations concludes as follows:

> In gastric ulcer, the gastroscope may reveal ulcers not otherwise demonstrable, and affords proof of healing more cheaply and accurately than any other method.
>
> In chronic gastritis, gastroscopy provides confirmation not otherwise obtainable and enables differentiation of type and degree of severity, essential for satisfactory disposal and treatment. Mucosal atrophy can only be diagnosed with any degree of certainty by gastroscopy.
>
> Multiple gastric erosions are only rarely demonstrable by x-rays, but by gastroscopy lesions of some significance can be diagnosed and differentiated into the chronic and acute, and disposal can be made accordingly.
>
> In other Service cases, less numerous but no less important, gastroscopy may offer the only means of diagnosis. These include early gastric carcinoma, benign gastric tumors, postoperative dyspepsia, unexplained gastric hemorrhage and achlorhydria.

Pollard and Lopes Pontes[62] have reached somewhat similar conclusions — namely, that gastroscopy and roentgenology, as the only direct diagnostic procedures for the detection of gastric ulcer, should be concurrently employed. Although x-ray examination reveals the lesion a little more frequently, gastroscopy appears to make it possible to discriminate between a benign and a malignant lesion in a higher proportion of cases. Both methods have their own limitations and so-called "blind spots." Gastroscopy is the only reliable method available for the diagnosis of a primary or associated gastritis. It is also of considerable help in the recognition of certain types of localized gastritis that roentgenologically may simulate a neoplastic formation.

Gastritis. Gray[63] studied the epigastric symptoms in alcoholic patients with and without gastritis and found that only 7 per cent of the group with normal stomachs had symptoms referable to the gastrointestinal tract, whereas 53 per cent of the patients with chronic gastritis and 60 per cent of those with severe gastritis had gastric complaints. It therefore appears from these studies that there may be a direct relation between gastritis and the incidence of symptoms in chronic alcoholic addicts.

In last year's report,[1] Benedict's[64] article on hypertrophic gastritis was reviewed. In a discussion of this paper Carey[65] stated that the picture closely agreed with his own experience in that the symptoms are similar to those of ulcer. Night pain and radiation of pain were seen less frequently by Carey than by Benedict.

Spriggs and Marxer,[66] in a monograph on polyps of the stomach and polypoid gastritis, state their belief that polyps are prone to malignant degeneration. Such a change was reported in between one in five and one in six of the series. The diagnosis of a polyp or polyps is made by radiology and, in suitable cases, by gastroscopy. Polypoid gastritis usually responds to treatment, which includes dietary measures, elimination of alcohol and in some cases gastric lavage.

Kantor[67] believes that positive gastroscopic evidence of gastritis in a front-line soldier should entitle him "to every consideration and to every benefit."

Gold[68] made a gastric study in 50 soldiers with dyspepsia and reported that gastroscopy is the only reliable method available for the study of

gastritis. Hemorrhage from gastritis is not a rare occurrence. Further studies, he says, are indicated regarding the incidence of gastritis in military forces, the effects of therapy and the interference of symptoms with the performance of duty.

Although it has been possible to correlate fairly accurately the gastric findings in gastritis with the post-mortem findings (Benedict and Mallory[69]), it may not be so easy to account for the symptoms on a pathological basis. In this connection Ortmayer[70] pointed out that it would be difficult to correlate such symptoms with relatively minor pathologic changes, such as nonulcerating gastritis, probably because the pain threshold of the stomach is high. Even a striking lesion, such as a deep gastric ulcer, may not produce symptoms. Ulcers may be painful on one day and not at all painful on the next. It is timely to emphasize in this regard, as Renshaw[71] and Wilkinson[72] have done, that patients as a whole, not "stomachs," are being treated.

Relation of chronic gastritis to cancer of stomach. A number of observers have stated that carcinoma of the stomach does not develop on a previously healthy mucosa. Many recent reports indicate that gastric atrophy predisposes to gastric carcinoma. Among these may be mentioned that of Shapiro, Schiff, Maher and Zinninger,[73] who found microscopic evidence of atrophic gastritis in 28 (80 per cent) of 35 cases of gastric cancer. They believe that the frequent coexistence of atrophic gastritis and gastric cancer strongly suggests a relation between them, the nature of which has yet to be determined.

Westhues,[74] on the basis of 463 resected stomachs and 40 stomachs obtained by autopsy, concludes that inflammation is not the decisive factor in the development of gastric cancer. The blastomatous gastric polyps, which are definitely precancerous in nature, are likewise not inflammatory, and cancers developing from them are not the result of inflammation. Westhues does not deny the possibility of development of cancer on the basis of gastritis.

Doehring and Eusterman[75] record the results of their observations on 40 patients with associated pernicious anemia and carcinoma of the stomach, studied at the Mayo Clinic. Of 1014 patients with pernicious anemia, 17 had carcinoma of the stomach, an incidence of 1.7 per cent, or slightly higher than that of gastric carcinoma in the general population. Carcinoma associated with pernicious anemia was found to be of a similar grade of malignancy and in the same location as carcinoma uncomplicated by pernicious anemia. Pernicious anemia usually sets in at about the age of fifty-four, while signs of cancer appear at the average age of sixty-three. Gastric carcinoma in association with pernicious anemia is becoming more frequent, probably owing to the fact that modern methods of treatment prolong the period of survival long enough for carcinoma to set in. Achlorhydria is invariably found with pernicious anemia and usually with gastric carcinoma. The cancer usually develops in the pyloric region. It develops with less frequency in the middle third of the stomach, and is most rarely discovered in the upper third. All the cases studied were adenocarcinoma. Benign tumors or polyps develop fairly often in cases of pernicious anemia.

White[76] reports a case of pernicious anemia of long standing in which both carcinoma and tuberculosis of the stomach were found at operation. This is the tenth verified case of gastric tuberculosis encountered at the clinic and the second verified case of carcinoma and tuberculosis in the same stomach. In commenting on this case, Walters[77] remarks that in pernicious anemia it is the associated gastritis that is of concern. Gastroscopists have offered additional proof of the possible precancerous nature of gastritis. Schindler[78] has found gastric adenomas in 6 per cent of the cases of atrophic gastritis, whereas these adenomas occurred in less than 1 per cent of cases in which atrophic gastritis was not present. In addition, adenomas of the mucosa occurred in 14 per cent of cases of pernicious anemia.

Brindley, Dockerty and Gray[79] report a case of multiple carcinoma of the stomach in which examination of the resected specimen revealed four adenocarcinomas of different degrees of malignancy. In this case diffuse advanced chronic gastritis may have been a precursor of the multiple carcinomatous lesions. Credence is given to this supposition by the diffuse nature of the chronic gastritis, particularly with reference to the pronounced hyperplasia of mucous cells, and by the presence of multiple lesions of all four grades of malignancy.

Freedman, Glenn and Laipply[80] report 5 cases of atrophic gastritis simulating gastric carcinoma. They emphasize that the localized form of hypertrophic gastritis may be difficult to differentiate from carcinoma. Even gastroscopically, this differentiation cannot always be made. The diagnostic difficulties were such that carcinoma could not be excluded before an exploratory laparotomy was done. In 3 of the cases, the true nature of the lesion did not become apparent until histologic examination of the resected specimens was made. Chronic gastritis is in some cases a curable precancerous condition. Patients should be carefully followed with repeated x-ray and gastroscopic examinations.

Gastric ulcer. In a discussion of the treatment of gastric ulcer, Judd and Priestley[81] point out that in certain cases all the main differential points between benign and malignant gastric ulcerations, including x-ray examination and gastroscopy, may be misleading. They believe that medical treatment of presumed gastric ulcer leaves much to be desired. The error in the preoperative diagnosis of gastric ulcer in differentiation from gastric can-

cer is approximately 10 per cent. Only approximately half the cases treated medically for gastric ulcer show results that these writers consider entirely satisfactory, and about 10 per cent of them subsequently prove to have carcinoma. The results of the surgical treatment of gastric ulcer are entirely satisfactory in the majority of cases. Since the operative mortality of gastric resection in Judd and Priestley's experience has been only 2.5 per cent, they are increasingly in favor of surgical treatment.

Duodenal ulcer. Tumen and Lieberthal[82] made gastroscopic studies of 50 patients with duodenal ulcer uncomplicated by pyloric obstruction. Of these, 33 had chronic gastritis, 1 had unclassifiable inflammatory changes and 16 had normal stomachs. The presence of gastritis did not regularly influence the clinical course of duodenal ulcer. It was impossible to postulate the presence or absence of associated gastritis on the basis of the nature of the symptoms or the character of the response to treatment.

Carcinoma. Schiff[83] believes that the diagnosis of gastric diseases has been greatly aided by the use of the gastroscope. In carcinoma it is helpful not only in detecting the presence of the tumor but also in determining its location, character and extent. The gastroscope is also of value in excluding the presence of cancer in suspected cases, thus frequently preventing unnecessary operation. The best results are obtained by co-ordinating the findings of gastroscopic and roentgenologic examinations.

Pack and McNeer[84] in a discussion of total gastrectomy for cancer point out the value of the esophagoscope and the gastroscope in determining the region of the growth either in the esophagus or in the stomach. If the x-ray studies show the upper third or more of the stomach to be pliable and apparently uninvolved, the flexible gastroscope may be safely introduced. It is often helpful in forming an idea concerning the amount of uninvolved stomach superior to the cancer. If the lesion extends high or if the esophagus is involved, the flexible gastroscope should not be used, because it is introduced blindly and so may traumatize the cancer and cause hemorrhage or perforation. The rigid esophagoscope of the Janeway or Jackson type is safer to employ under these circumstances, since it is passed down the esophagus under direct visual guidance at all times. Furthermore, it is possible to obtain a biopsy through this instrument. By measurement from the upper incisor teeth, one can determine the exact location of the superior margin of the cancer.

For several years partial gastrectomy by the transthoracic approach has been recognized as an outstanding contribution to gastric surgery. Sweet[85] has recently reported 7 cases of total gastrectomy by the transthoracic route. Diagnostic esophagoscopy and gastroscopy in addition to x-ray examination may be extremely helpful in establishing the diagnosis and planning the surgical approach and in determining operability. Peritoneoscopy is also important as a means of excluding liver metastases before major surgery.

Experimental studies. Paul[86] studied 107 patients with normal gastric mucosa by gastroscopy and found that acetylsalicylic acid caused no hyperemia, edema or hemorrhage even in daily doses as high as 80 gr. The ingestion of the drug over long periods of time does not produce chronic gastritis, and the epigastric distress that sometimes occurs after the ingestion of acetylsalicylic acid may be the result of increased acid production and pylorospasm.

Layne and Carey[87] made an endoscopic study of the appearance of the gastric mucosa in the anesthetized dog, concluding as follows:

> The presence of foreign material or food in the stomach causes an appearance of hyperemia with congestion and excess secretion of mucus.
>
> Inflation flattens the mucosal folds and often brings blood vessels into view.
>
> A diet of coarse food, such as hospital scraps, produces hyperemic, granular changes in the gastric mucosa. The gastric mucosa appears normal only when the dog is fed dog biscuits.
>
> Atropine decreases the quantity and changes the character of gastric secretion and diminishes gastric tone.
>
> Pilocarpine augments the amount of gastric secretion and increases gastric tone.
>
> Benzedrine produces transient hyperemia of the gastric mucosa and decreases gastric tone slightly.
>
> Alcohol induces generalized hyperemia of the gastric mucosa, which subsides after about five weeks. The gastric mucosa thereafter remains normal even with continued administration of alcohol.

Although it is manifestly impossible to review adequately the volume by Wolf and Wolff[88] entitled *Human Gastric Function*, this report would not be complete without mentioning the importance of their contribution. This book is based on a study of a patient with an esophageal stricture who had fed himself through a gastric fistula for forty-seven years. It is a modern continuation of the work of Beaumont, Richer and Carlson, with special reference to the significance of the psychosomatic influences on gastric functions. The character of the subject's defect offered an excellent opportunity for a prolonged close inspection of the stomach mucosa by virtue of the large size of the defect and also because of the collar of mucous membrane that lay exposed on the abdominal wall. Changes in vascularity were readily recognized by variations in the color of the mucous membrane. Accelerated blood flow in the mucosa was not merely associated with blushing of its surface; the membrane itself became wet, swollen, and turgid, and the rugae were slightly fuller and smoother. These evidences of vascular engorgement were especially obvious in the collar of mucosa exposed on the abdominal wall. During marked hyperemia, it often doubled in thickness (from 5 to 10 mm.) and its radial folds

decreased in number from twelve or thirteen to five to seven. The tissue itself under such circumstances felt succulent and boggy.

The correlation of motor activity and blood flow was demonstrated under different conditions, such as distention of the stomach, mechanical irritation, ingestion of food and swallowing. Hyperfunction of the stomach, either motor or secretory, was always accompanied by hyperemia.

Varying emotional states may be associated with profound alterations in gastric functions. In the evaluation of the effects of drugs, the prevailing affective state of the patient at the time, the circumstances surrounding the experiment and the patient's reaction to the mode and implication of the administration of the drug, as well as his reaction to its side effects, were found to be of first importance.

Changes in gastric function in reaction to various situations and accompanying emotional states are presented in detail. Observations on the collar of the mucosa were made during a discussion of appetizing foods, alarm reaction (fear), depressive thoughts, resentment, hostility, anxiety and so forth. The alterations in gastric function fell into two categories: depression of acid output, motor activity and vascularity; and acceleration of these functions. The former was associated with a reaction of flight or withdrawal from an emotionally charged situation. The latter accompanied a reaction of internal conflict, with an unfulfilled desire for aggression and fighting back. Profound and prolonged emotional disturbances of this kind were accompanied by marked and prolonged increases in gastric motility, secretion and vascularity, with reddening and engorgement of the mucous membrane, often reproducing the picture of gastritis. This picture was induced by vasomotor changes resulting in hyperemia and congestion of the mucosa. The protective power of mucus was demonstrated. An appearance simulating chronic peptic ulcer was produced by exposing a peripheral edge of the collar of mucosa continuously to the digestive action of gastric juice for four days. After the ulcer and the surrounding area had been covered with a protective petrolatum dressing, complete healing took place within three days, leaving no trace of the lesion.

The following conclusions were rendered from this study:

> Undue and prolonged acceleration of acid secretion in the stomach, however provoked, resulted in hyperemia and engorgement of the mucous membrane resembling hypertrophic gastritis. The mucosa in this state was unusually susceptible to injury, and even the most trifling traumas resulted in hemorrhages and small erosions. Ordinarily the mucosa was protected from injury by an effective coating of mucus; loss of this protection in the face of minor traumas led to edema, inflammatory changes, erosions and hemorrhages. Contact of acid gastric juice with a denuded surface induced further hyperemia and acceleration of acid secretion. Prolonged contact of acid gastric juice with a minor erosion resulted in the formation of a peptic ulcer.

Peritoneoscopy

Technic. Harken and Glidden[89] used transparent collapsible plastic balloons in various sizes and shapes on the cardioscope. These balloons may be applicable for peritoneoscopy, as suggested by Lamb[90] in 1941.

Cirrhosis. One of the most valuable uses of the peritoneoscope is in the study of cirrhosis of the liver and the differential diagnosis from carcinoma. In this connection it is interesting to note the frequency of cirrhosis of the liver as reported by Peller.[91] This author found among the records of 6596 cases in the Bellevue Hospital, New York City, covering the period from 1934 to 1941, cirrhosis of the liver in 9 per cent of the patients over twenty years of age. Malignant tumors were found in 17 per cent of these patients.

Amberg[92] discusses the prognosis of chronic hepatitis in children, stating that early acute hepatitis usually heals. It may progress and develop into diffuse necrosis of the liver, of which acute, subacute, subchronic and chronic forms have been distinguished. The chronic form has been interpreted as healing of the necrosis with development of cirrhosis of the liver. Cirrhosis has been defined as a progressive lesion that involves parenchymatous degeneration and fibrous and parenchymatous repair and sooner or later causes death. Unfortunately, most of the cases of chronic hepatitis that Amberg encountered were of this kind. In summary, the author reports that chronic hepatitis of children ending in cirrhosis fairly frequently extends over a period exceeding five years. It seems possible that the disease need not always end in cirrhosis but may heal. In my opinion, information regarding hepatitis and cirrhosis in children as well as in adults will be obtained by the increasing use of peritoneoscopy together with biopsy of the liver.

Kirshbaum and Shure[93] have reported 356 autopsy cases of alcoholic cirrhosis. The ratio of males to females was 2:1. In 42 per cent of the cases, a history of chronic alcoholism was obtained. Jaundice was present in 48 per cent, and ascites in 59 per cent. Hypertrophic livers were noted in 62 per cent, and atrophic livers in 38 per cent. All the spleens were enlarged. In 11 cases, primary carcinoma of the liver was encountered as an incidental finding.

Ascites. Meigs, Armstrong and Hamilton[94] have listed 27 cases of fibroma of the ovary with fluid in the abdomen and chest — Meigs's syndrome. The syndrome is of considerable importance, because some patients have failed to obtain proper surgical relief, whereas others, originally doomed because of a tumor considered inoperable, are now well. Undoubtedly peritoneoscopy would be of value in the diagnosis of some of these cases, especially in the differentiation of this condition and carci-

nomatosis, tuberculous peritonitis, cirrhosis of the liver and other diseases in which ascites may be present.

Jaundice. White[95] has made a study of errors in the diagnosis of jaundice, limiting his paper to 175 cases that came to operation or autopsy. Peritoneoscopy was used in only a small number of cases. Over half the errors were associated with a diagnosis of cancer. Too many diagnoses of cirrhosis were made when latent cancer was present. Errors in diagnosis were made in 14 cases (8 per cent). Judging from the kind of errors reported, it is evident that a more frequent use of the peritoneoscope would have eliminated many of them.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30221

PRESENTATION OF CASE

A fifty-three-year-old housewife entered the hospital because of right-sided paralysis.

The patient was known to have had hypertension. Six or eight months before entry she was seen in the Eye and Ear Infirmary for cataract and possible separation of the left retina. The day before admission she suddenly found herself unable to speak. She then developed paralysis of the right side of the body. No other information was available.

Physical examination showed a well-developed, obese woman who was unable to speak but who appeared conscious of her surroundings. A mature cataract of the left eye was present. There was flaccid paralysis of the right leg. The right arm and hand moved only slightly. There was no facial asymmetry. The biceps, triceps, radial and ankle tendon reflexes were decreased on the right. The right patellar reflex was absent. The plantar reflexes were decreased on the right and increased on the left. There was no Kernig sign. A questionable right temporal hemianopsia was present. She could not swallow. Ophthalmologic examination showed the right fundus to have an old hemorrhage at ten o'clock. The vessels were tortuous. There was arteriovenous nicking. The left fundus could not be visualized. The heart was rapid. No other findings were recorded.

The blood pressure was 200 systolic, 125 diastolic. The temperature was 100°F., the pulse 120, and the respirations 25.

Examination of the blood showed a white-cell count of 21,400. The urine was acid, with a specific gravity of 1.024 and a + test for albumin. The sediment was negative. A blood Hinton test was negative. The nonprotein nitrogen was 27.5 mg. per 100 cc.

The patient was given 500 cc. of 5 per cent dextrose in saline intravenously the first day, and between 700 cc. and 1500 cc. of the fluid daily thereafter. She was fed by an indwelling Levine tube. On the sixth hospital day she developed diarrhea, which may have been due to an intake of 200 cc. of fluid by mouth at one time. Her condition otherwise remained essentially the same until the ninth hospital day, when the temperature rose to 103°F., the pulse to 136, and the respirations to 40; the blood pressure fell to 110 systolic, 88 diastolic. Examination at that time showed rapid, grunting respirations. The face was flushed. The lips and nails were cyanotic. There was herpes on the lips, and some jaundice. Many coarse, snapping rales were heard at the left base posteriorly and over the axilla, without dullness. The point of maximal cardiac impulse was felt 11 cm. to the left of the midline. The rate was rapid. The aortic second sound was equal to the pulmonic. No murmurs could be heard. The abdomen was negative. The right leg was edematous, with tenderness in the calf and a positive Homans's sign. The right superficial femoral veins were hard and tender medially above the knee.

A portable x-ray film of the chest showed questionable dullness over the left midlung field, but this could not be definitely determined. Femoral-vein ligation was deemed inadvisable. The patient was given 5 gm. of sulfadiazine intravenously on the ninth and tenth days and 2.5 gm. on the eleventh day. On the twelfth day the urinary output fell to 500 cc. on an intake of 1500 cc. The blood sulfadiazine level on the twelfth day was 40 mg. per 100 cc. The temperature came down to normal, but the urinary output remained low. Intravenous fluids, sodium lactate and high intravenous vitamins failed to affect urinary excretion. The sulfadiazine level was 9 mg. per 100 cc. on the fifteenth hospital day. On the seventeenth hospital day she became stuporous. The nonprotein nitrogen was 89 mg. per 100 cc., and the protein 6.7 gm. She became comatose and died on the eighteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR WATKINS: In this case we are called on to explain a sudden right hemiplegia followed by death eighteen days later. The only information in the past history reveals a hypertension of unknown duration and a cataract of some eight months. The latter I cannot connect with the final illness. The hypertension, however, I should expect to have been directly responsible for the symptoms — the loss of speech followed by right hemiplegia within a day and unassociated with loss of consciousness. The speech loss alone might have been due to a relatively discrete lesion in the motor speech area of the cortex in the left frontal lobe in a right-handed patient. This could have been embolic or due to a small hemorrhage or thrombosis. A rather complete right hemiplegia developed within twenty-four hours, and if also due to a cortical lesion it would have involved an area sufficiently large, one would presume, to have caused loss of consciousness. It seems more likely that the hemiplegia was due to hemorrhage in the internal capsule.

*On leave of absence.

I am not given sufficient data to distinguish between cortical or subcortical types of aphasia, or for speech loss due to a bulbar lesion. To connect it with the hemiplegia, the lesion could have been subcortical. There was a complete flaccid type of paralysis of the lower extremities — often seen in the early stages of hemiplegia — and nearly complete paralysis of the upper extremity. The fact that the leg was more involved than the arm also points to a subcortical lesion, as the cortical areas for speech and leg movement are quite separated.

In view of the acute onset and the known vascular disease, I can see no reason to consider brain tumor. There was no facial asymmetry, presumably, at rest. I would like to know if the movements were normal. It seems unlikely to me that they were. We are told nothing of the other cranial-nerve functions. The tendon reflexes were diminished or absent, which is in keeping with the flaccid type of paralysis. The description of the plantar reflexes is ambiguous. Without knowing whether the movement of the great toe was an inflection or an extension, I can only guess that there was a slight plantar reflex or Babinski on the right, and a quite definite one on the left. Both reflexes were therefore pathologic. If this assumption is correct, it is of great importance in localization.

The patient was unable to swallow although conscious, which is an unusual finding in hemiplegia. One immediately suspects a bulbar palsy from involvement of the nucleus of the lower cranial nerves. In such a case the lesion would have to be below the level of the seventh nerve. With complete paralysis one would expect a contralateral sensory loss. We do not know anything about the sensory findings and they would have been hard to test in this patient.

A most significant finding was the right temporal hemianopsia. This immediately locates the lesion above the brain stem, probably in the optic radiations. Hemianopsia in this area, however, would not cause loss of swallowing because of the bicortical representation of the cranial nerves. I therefore conclude that there was bilateral involvement of the cortical tracts, giving a pseudobulbar palsy, which conforms with the bilateral Babinski tests.

There was a well-marked hypertension, and vascular changes in the eye grounds, but not much evidence of renal failure as judged by subsequent urine examination, with good concentration, a + test for albumin and a negative sediment and by a normal nonprotein nitrogen. On admission, one would presume that the likeliest diagnosis was hypertension with a cerebral vascular accident — chiefly either hemorrhage or thrombosis of the left internal capsule but with some damage to the right side of the brain. There was no evidence of valvular heart disease, and there was no apparent source of emboli elsewhere in the body.

On the ninth hospital day there was a sudden change, which is about the time that we begin to look for pulmonary complications in patients with hemiplegia who are not getting well. In this case the pulmonary embarrassment was quite severe and there was circulatory collapse as well, with a fall in blood pressure and a rapid pulse. There were rales in the left base, and dullness. The heart was not enlarged to palpation. No mention is made of pain, cough or bloody sputum, but I still suspect pulmonary infarct. Examination of the extremities then revealed an edematous right leg, with a tender calf, and a positive Homans's sign, — pain in the popliteal space on dorsiflexion of the foot, — which at once suggests phlebothrombosis. The superficial femoral veins were hard and tender. She had fever, however, and it might have been a thrombophlebitis. I suspect the pulmonary signs were due to an embolus. The portable chest plates apparently were inconclusive.

The thrombophlebitis developed in the paralyzed leg during the first week in bed. Because of the fever I presume that it was thought that the patient had an infected pulmonary embolus or a bronchopneumonia, and sulfadiazine was given. On the third day there was diminished urinary output and an extremely high blood diazine level. In spite of intravenous fluids, the urinary excretion did not increase, the patient became comatose, and the nonprotein nitrogen rose to 89 mg. per 100 cc., and nine days following the administration of the sulfadiazine the patient died. We do not know whether there was crystalluria or hematuria. She had one negative urine examination on admission, and it is possible that the renal failure was due to sulfadiazine that had precipitated and had caused renal obstruction. There is no history of pain or swelling in the kidney region. Perhaps it is unusual to have signs of renal complication develop after only three days of sulfadiazine. I have recently, however, seen reports of cases in which intravenous diazine was given routinely to surgical patients in exactly the same dosage, 43 per cent of whom developed renal complications when alkaline therapy was not given. So it seems possible that there was a renal complication due to the precipitation of sulfadiazine crystals, with obstruction. There may have also been a toxic nephritis. We do not know whether she had had sulfa drugs previously; perhaps this would have been more likely if she had had some. Another possibility is thrombosis of the renal vessels. The patient probably did have a certain amount of acidosis; she was dehydrated and had diarrhea, which makes renal complications likelier under sulfadiazine treatment.

I therefore conclude that the patient had a cerebral vascular accident which chiefly consisted of hemorrhage or thrombosis — I cannot be sure which — into the left internal capsule; there was possibly some similar involvement on the right, resulting in a pseudobulbar palsy. She had hyper-

tension, arteriosclerosis, thrombophlebitis of the right femoral vein, with pulmonary infarction, and renal obstruction due to sulfadiazine, possibly with a toxic nephritis and some thrombosis of the renal vessels.

DR. AUGUSTUS ROSE: Have you any preference between thrombosis and hemorrhage?

DR. WATKINS: Without loss of consciousness, one would probably say that thrombosis was likelier to be the cause, particularly after such an extensive hemiplegia. But a slow type of hemorrhage might do the same thing.

DR. WYMAN RICHARDSON: I think that Dr. Watkins should protect himself against the machinations of the Pathology Department by mentioning the fact that we had one patient who had a paradoxical embolus to the brain through a patent foramen ovale. I am not suggesting that as the cause here, but it should be mentioned.

DR. ROSE: Occasionally, cerebral emboli occur without a patent foramen ovale and with relatively little in the way of pulmonary involvement.

DR. BENJAMIN CASTLEMAN: Emboli from pulmonary veins?

DR. ROSE: Yes. The leg vein is responsible for a pulmonary embolus, and another embolus is released from a thrombosed pulmonary vein in the infarcted area.

DR. CASTLEMAN: I do not remember any such cases, although it would be hard to prove.

DR. ROSE: You read about them in the textbooks.

DR. CASTLEMAN: We had a case of cerebral embolus some time ago in which we wondered about the possibility that the embolus had arisen from a pulmonary vein close to a pneumonic area.

CLINICAL DIAGNOSES

Hypertensive heart disease.
Uremia.
Thrombophlebitis.
Right hemiplegia, with aphasia.

DR. WATKINS'S DIAGNOSES

Cerebral thrombosis or hemorrhage: large lesion in left internal capsule, small one in right internal capsule.
Hypertensive heart disease.
Thrombophlebitis of right femoral vein.
Pulmonary infarction.
Renal obstruction due to sulfadiazine crystals.

ANATOMICAL DIAGNOSES

Cerebral hemorrhage.
Pulmonary embolism, acute, massive.
Bronchopneumonia.
Pulmonary congestion and edema.
Pulmonary infarct, minute.
Central congestion and necrosis of liver.
Thrombosis of right posterior tibial and popliteal veins.
Cardiac hypertrophy, hypertensive type.
Jaundice.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient showed a thrombus in the right posterior tibial and popliteal veins. It had in part broken off and produced a massive pulmonary embolus of the left pulmonary artery, which was probably the immediate cause of death. There were a few smaller emboli in the lungs, but only one small infarct, which measured about 2 by 1 cm. There were, however, scattered foci of bronchopneumonia and edema and congestion of the lungs. The kidneys showed a moderate degree of vascular nephritis but no evidence, so far as we could make out, of sulfonamide changes.

Dr. Kubik will describe the cerebral findings.

DR. CHARLES S. KUBIK: There was a hemorrhage, measuring 5 cm. in diameter, in the left frontal lobe. It was farther forward than usual, destroying the head of the caudate nucleus, and displacing the internal capsule and lenticular nucleus backward. It had not ruptured into the lateral ventricle or subarachnoid space. A large part of the clot was brick red and rather firm, obviously representing old hemorrhage; another part consisted of the usual soft, gelatinous, dark-purplish clot of recent hemorrhage. Thus there were at least two episodes of bleeding. There were several small old infarcts, up to 3 or 4 mm. in diameter, in each lenticular nucleus. Such lesions are a frequent finding in long-standing hypertension, and do not, as a rule, cause obvious symptoms or abnormal neurologic signs. I do not know how to explain the left-sided extensor plantar response. There was no associated hemorrhage of the midbrain or pons.

I might add that this patient survived an unusually long time. In most cases of massive cerebral hemorrhage* death occurs in from a few hours to two or three days, though occasionally not until a week or ten days. Recovery almost never takes place. I believe that only two old cerebral hemorrhages have been found at autopsy at this hospital in the past fifteen years. Patients who survive a severe "shock" and are left with a residual hemiplegia or hemiparesis may, with rare exceptions, be assumed to have had a cerebral infarct.

DR. WATKINS: When do you think the pulmonary embolism occurred?

DR. CASTLEMAN: The massive one probably occurred within twenty-four hours of death. The patient may well have had one on the ninth day, associated with the fall in blood pressure and cyanosis.

*A distinction is made between cerebral hemorrhage, originating within the substance of the brain, and subarachnoid hemorrhage. In the latter condition, which usually results from a leaking aneurysm, the death rate is comparatively low, probably between 25 and 30 per cent, at the time of the first attack.

It is interesting to speculate concerning the cause of the jaundice. Ordinarily when a patient with cardiac disease develops jaundice, the first thing to be considered is infarction of the lung. The jaundice is believed to be due to the inability of a congested liver to excrete the excess bilirubin produced by the hemolysis of the red cells in the infarct. Although this patient had emboli to the lung, there was only one small infarct. It is conceivable, I suppose, that the absorption of bilirubin from the cerebral hemorrhage, which had existed for eighteen days, might have been a factor in the production of the jaundice. The liver was only moderately congested; there was some central necrosis with fatty vacuolization, but not any more than one sees in many patients without jaundice.

DR. RICHARDSON: I do not believe that absorption from the cerebral lesion was enough to have caused jaundice.

DR. CASTLEMAN: Ordinarily, I should not have thought so, but it was a large hemorrhage of eighteen days' duration.

CASE 30222

PRESENTATION OF CASE

A sixty-two-year-old housewife entered the hospital because of intermittent, severe pain in the lower part of the back of seven days' duration.

The patient was in good health until about two years before entry, when she suddenly developed severe, boring pain across the upper abdomen, with nausea and vomiting of recently ingested food. The pain gradually subsided. She was asymptomatic for two weeks, and then had a recurrence of the pain, as well as the nausea and vomiting, lasting from twelve to twenty-four hours. Similar attacks recurred every three to six weeks until three months before admission, when they entirely ceased. She had no hematemesis or tarry or bloody stools. She was markedly constipated, requiring regular catharsis. A gastrointestinal series one year and three months before entry was said to have been negative.

Four weeks prior to admission she developed slight frequency and nocturia (two to four times), with a drawing, mild, nonradiating pain just above the symphysis on urination. These symptoms persisted. There was no hematuria or pyuria. At the same time she noticed brownish irregular spots in the left upper visual field. Seven days before admission she developed an intermittent, severe, burning pain in the right costovertebral angle and low back, which persisted.

She had lost 30 pounds in two years, "most of it in the past five months." She had had considerable weakness and fatigue in the two-year period, as well as occasional cramps in the muscles of the extremities. About a year and a half before admission, in a community hospital, she had a right radical mastectomy for carcinoma of the breast. Since then her physician had treated her with iron and liver for "anemia."

Physical examination showed a somewhat undernourished woman. The right radical mastectomy scar was well healed, and there was no evidence of recurrent carcinoma in the scar or in the axilla. Some lymphedema of the right arm was present. The lungs were clear. There was a hard, lobulated mass occupying the entire lower abdomen, being more pronounced on the right side and extending 5 to 7 cm. above the symphysis. It was stony hard and lobulated, and seemed fixed to the pubic ramus. Pelvic examination showed a small cervix. The uterus was normal in size and anteriorly situated. Behind it and to the right was the above described mass, which measured 8 cm. in diameter and was adherent to the vagina and partially fixed in the pelvis.

The blood pressure was 140 systolic, 75 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 2,770,000, with 8.2 gm. of hemoglobin. The white-cell count was 10,000, with 84 per cent neutrophils. The urine was negative. The sedimentation rate was normal. The stools gave a ++++ guaiac test. A blood Hinton test was negative.

X-ray examination of the chest, spine and gall bladder, as well as the plain films of the abdomen, was negative. An intravenous pyelogram showed prompt excretion of the dye by both kidneys, outlining a nondilated pelvis, calyxes and ureters on the left. The right renal pelvis and calyxes were moderately dilated, and the terminal calyxes blunted. The upper half of the right ureter was well visualized and showed slight dilatation. The remainder was not definitely visible below the level of the fifth lumbar vertebra, except for a small segment just about the ureterovesical junction. A pressure defect on the right side of the bladder was present, apparently due to a soft-tissue mass occupying the right side of the pelvis. A cystoscopy showed a pale bladder mucosa. In the right base the wall was apparently pushed in by an extrinsic mass forming a projection 4 by 5 cm. The right ureter looked normal and was easily catheterized for 5 cm., when considerable urging was required. It finally passed about half way to the kidney and drained clear urine. A retrograde pyelogram showed the right ureter to be tortuous, with a rather sharp angle opposite the fourth lumbar vertebra. The ureter appeared narrow just below the sacroiliac region. No calculi were visible.

The patient was given several transfusions, and on the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.: May we see the x-ray films?

DR. MILFORD SCHULZ: These films show slight dilatation of the pelvis, calyxes and upper ureter on the right side. Here is the shadow of the mass occupying the right side of the pelvis, which may be responsible for the delayed emptying and abnormal filling of the kidney and ureter. There is nothing remarkable in the films of the chest except for evidence of the old mastectomy.

DR. HAMLIN: We are asked to determine the nature of a mass in the abdomen. I can make little out of the past history. The episodes of nausea and vomiting and of pain in the abdomen over the two years previous to entry seem rather typical of intestinal obstruction, but not much else. It is fortunate that this mass did cause pressure on the bladder and the ureter, because apparently that was the only reason the patient entered the hospital. The mass was said to occupy the entire lower abdomen but extended only 5 to 7 cm. above the symphysis. By pelvic examination it was more on the right side, and measured 8 cm. in diameter.

In attempting to determine the nature of such a mass, one can look at it from the anatomic point of view. Where could this mass have arisen? The first thing one thinks of is the uterus. This is ruled out because the pelvic examination showed a normal uterus. One next thinks of the ovary. That cannot be ruled out, and must be further considered. It may have been a mass attached in some way to the intestine. The positive guaiac test makes that appear somewhat likely. It might also have been a retroperitoneal mass of some form, lymphoma or neurofibroma or something of that nature. One must think of a bone tumor, but in the absence of x-ray evidence of bone involvement one can safely rule that out. Under the circumstances, it seems a little unusual that they did not attempt a barium enema, because it would seem that more information could have been gathered from that than from anything else.

The next question one should decide is whether this was a malignant or a benign lesion. The cachexia, the weight loss, the pronounced anemia and perhaps the stony hardness of the mass, as well as the rapidity with which the symptoms developed, make one lean strongly toward a malignant tumor. The consistence of the mass is rather less in favor of the usual retroperitoneal mass than it is of tumor of some other origin, although retroperitoneal masses may be extremely hard. Therefore, I should like to consider that it was an intraperitoneal malignant tumor, and that leads us back to a tumor of the ovary or of the intestine. I see no way of ruling either of these possibilities in or out. The positive guaiac test in the stool makes one think that it might have been a tumor that had either eroded into the intestine or arisen from the intestine, causing some bleeding. On the other hand we already know that she had had a carcinoma of the breast, and one of the rarer but not too uncommon sites of metastases of carcinoma of the breast is to the ovary. A case came to my knowledge recently of a woman with carcinoma of the breast who had had the tumor removed several years before but had developed many bone metastases and had also developed large tumors in the pelvis. It was with some interest that the physician noticed a considerable regression of the bone metastases as the tumors of the pelvis became larger, and finally at autopsy it was found that the metastases from the breast to the ovaries had completely replaced the ovaries, thus causing physiologic castration; the regression of the bone symptoms was attributed to that. So I should like to make a diagnosis of carcinoma of the breast metastasizing to the ovaries.

DR. FREDERIC B. MAYO: Could this have been a Krukenberg tumor? If not, why not?

DR. HAMLIN: I should think that it could have been.

DR. BENJAMIN CASTLEMAN: From a primary cancer of the stomach?

DR. MAYO: Yes.

DR. HAMLIN: The description of the tumor does not exactly bring a Krukenberg tumor to mind.

DR. CASTLEMAN: Most of the Krukenberg tumors are bilateral.

CLINICAL DIAGNOSIS

Carcinoma of ovary?
Carcinoma of intestine?

DR. HAMLIN'S DIAGNOSIS

Metastatic carcinoma of ovary from previous carcinoma of breast.

ANATOMICAL DIAGNOSIS

Malignant lymphoma, clasmatocytic type, of ileum, with extension into right ovary.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: It is not surprising that Dr. Hamlin was unable to decide where to place the tumor, — ovary or intestine, — because both were involved. The primary lesion was in a loop of ileum, the whole circumference of which for a distance of 11.5 cm. was replaced by a fleshy, smooth, pinkish-gray tumor, involving the entire wall and containing numerous areas of mucosal ulceration. The tumor in the ileum was attached to and had invaded the right ovary. Together they formed the mass in the right pelvis, and this was removed.

Microscopic examination showed it to be a very cellular tumor of the malignant lymphoma group, which we classified as belonging to the clasmatocytic or reticulum-cell sarcoma type. One would have liked to compare this tumor with that of the original breast tumor. It is conceivable that the original tumor was a lymphoma, but it is more likely that the patient had two tumors.

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THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

"EXPERT MEDICAL TESTIMONY"

A RECENT note in the April 1 issue of the *Journal of the American Medical Association* comments favorably on the attitude taken by the Minnesota State Medical Association, which three years ago appointed a committee on medical testimony to which could be referred instances in which physicians had given questionable testimony. This committee, after investigation and according to the facts, "may censure the physician, may publicize the circumstances of the particular case or may bring the matter to the attention of the state board of medical examiners for disciplinary action." A case is cited that had been investigated by the committee and referred to the board of medical examiners; the testifying physician, having been adjudged to have given unjustified testimony, was censured.

So-called "expert medical testimony" as given in court has long been a just cause of embarrassment to physicians, who consider much of it to be a discredit to a generally honored profession. There are no undisputed rules by which qualification as an expert can be judged, and contradictory testimony is frequently given by presumably equally qualified physicians. Furthermore, neither the medical profession nor the legal profession has interested itself in this important problem to the point of actually seeking results.

The concluding paragraph of the note in the *Journal of the American Medical Association* is worth reprinting for its uncompromising clarity.

> Next to saving life and giving aid to the sick and injured no greater responsibility devolves on the medical profession than giving testimony in court or elsewhere. The right of a physician to continue in the practice of medicine is measured not only by his professional competence as a physician but also by what he says and does as a physician.

In 1936 the Council of the Massachusetts Medical Society appointed the Committee to Consider Expert Testimony, thus anticipating the action of the Minnesota State Medical Association by five years. Unfortunately, although the Minnesota committee appears to be functioning in a spirited and effective fashion, the only fruit that this appointment has borne in eight long years has been an occasional meager report of progress. Meanwhile the battles of the "experts" continue.

SECONDARY STREPTOCOCCAL WOUND INFECTION

EPIDEMICS of secondary streptococcal infections of open wounds, such as burns, or of those following so-called "clean" operations are regularly experienced, particularly during the late fall, winter and early spring, by even the most expertly conducted surgical services. The usual reaction of the surgeon is to blame the sterile materials that he had used at operation, and the bacteriological laboratory is invariably swamped with requests for the cul-

turing of instruments, catgut and dressings. Recent investigations, however, have proved that such material is rarely, if ever, the cause of the difficulty.

Since it is well known that during the winter months the incidence of throat infections due to beta-hemolytic streptococci and the number of apparently healthy persons who are carriers of these organisms are higher than they are in the summer months, it is logical to connect this prevalence with epidemics of secondary wound infection. The organisms may be seeded in several ways — by droplet infection at the time of operation and by dust or droplet infection when dressings are changed in the ward. The persistence of beta-hemolytic streptococci, as well as that of diphtheria bacilli, in dust has been demonstrated by a number of British investigators during the past five years. Garrod* has recently shown that the dust from wards where there are patients with streptococcal infections may contain these organisms in large numbers, particularly the dust near the beds of infected patients, that dust from poorly lighted areas is likelier to contain streptococci than is dust from sites on or close to windows and that virulent beta-hemolytic streptococci can persist in the dark in naturally infected dust for as long as one hundred and ninety-five days.

Prevention or elimination of secondary streptococcal wound infection calls for a meticulous routine. Efficient face masks should be worn by all members of the operating team. All personnel intimately concerned with operations or with the dressing of wounds should be tested weekly — or immediately if they develop a "cold" or sore throat — for the presence of beta-hemolytic streptococci in the nasopharynx, and they should be excused from these duties if the cultures are positive. If possible, all patients who develop streptococcal infections or who are carriers should be isolated. Ideally, the ward should be sunny. The floors should be oiled, and no sweeping or dusting should be permitted in the hour preceding the time when dressings are changed. No visitors should be admitted to the ward and activity within the ward should be restricted during the dressing period. Finally, all new dressings should be handled only with sterile instruments, and these should be resterilized, or a new set used, for each patient. In the meantime, every surgeon should reconsider his technic from the point of view of decreasing the frequency of dressings. It has been shown, particularly in cases of burns, that, by using bulkier and more efficient dressings, they need not be changed oftener than once in two to four weeks, and in this way the danger of infection, as well as the amount of work, can be greatly reduced.

All these precautions undoubtedly cannot be taken at the present time, owing to the shortage of manpower. They offer, however, a goal to be attained, and many of them are relatively simple procedures whose adoption would accomplish much in lowering the incidence of secondary streptococcal wound infection.

*Garrod, L. P. Some observations on hospital dust. *Lancet* 1:245-247, 1944.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GRAVES — Word has been received of the death in the Pacific area of Lt. Commander Sidney C. Graves, U.S.N.R., formerly a prominent Boston gynecologist. His home was at 600 Brush Hill Road, Milton. He was in his forty-third year.

Dr. Graves received his degree from Harvard Medical School in 1929. He was assistant visiting surgeon at the Free Hospital for Women in Brookline and assistant in gynecology at the Harvard Medical School.

He was a fellow of the American Medical Association, a member of the American College of Surgeons, the New England Obstetrical and Gynecological Society and the Obstetrical Society of Boston and a diplomate of the American Board of Obstetrics and Gynecology.

His widow and three children survive.

HOWE — Harry N. Howe, M.D., of Greenfield, died May 11. He was in his seventy-third year.

Dr. Howe received his degree from Columbia University College of Physicians and Surgeons, New York, in 1899. He was president of the Franklin District Medical Society from 1916 to 1917. He was a member of the American Medical Association.

His widow survives.

MacDONALD — Frederick L. MacDonald, M.D., of Waltham, died May 24. He was in his sixty-sixth year.

Dr. MacDonald received his degree from the University of Vermont College of Medicine in 1907. He was the mayor of Waltham from 1934 to 1938. He was an instructor at Tufts College Medical School, on the staff of the Waltham Hospital and associated with the Massachusetts Eye and Ear Infirmary. He was a member of the American Medical Association.

A daughter and a granddaughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

Clinic	Date	Clinic Consultant
Lowell	June 2	Albert H. Brewster
Salem	June 5	Paul W. Hugenberger
Haverhill	June 7	William T. Green
Brockton	June 8	George W. Van Gorder
Worcester	June 16	John W. O'Meara
Pittsfield	June 19	Frank A. Slowick
Springfield	June 21	Garry deN. Hough, Jr.
Fall River	June 26	Eugene A. McCarthy
Hyannis	June 27	Paul L. Norton

WAR ACTIVITIES

INDUSTRIAL HYGIENE

Ethylene Chlorohydrin Poisoning

A workman in a Los Angeles manufacturing plant, while cleaning trays upon which rubber strips were stored, used a petroleum hydrocarbon solvent of the kerosene range. The supply of the solvent being temporarily exhausted, the man then used anhydrous ethylene chlorohydrin for the same purpose. He was careful to wear impervious rubber gauntlets. The room was large and well ventilated, but he was exposed to the vapors of the solvent.

When, after two hours, the workman became very ill, he was taken to the dispensary and five hours later removed to the hospital, where he died, eleven hours after he first started to use the solvent. The man was sixty-one years of age and in excellent physical health up to the time of this illness. It was found on investigation that he had been exposed to an average concentration of vapor of about 1 mg. per liter of air (305 p.p.m.).

Six white mice were exposed to a similar atmosphere and all were ill in an hour, with a downhill course after two hours. Exposure was then ended, and four hours later one of the mice died while the others were extremely ill. In twenty-four hours, the 5 mice were again normal.

Autopsy of the deceased, evaluation of the exposure and duplication of the exposure in laboratory animals with similar pathological findings, led to the conclusion that death was due to anhydrous ethylene chlorohydrin, proving that the solvent is dangerous even in relatively low vapor concentration. — Reprinted from *Industrial Hygiene News Letter* (April, 1944).

CORRESPONDENCE

PHYSICIAN NEEDED FOR BOY SCOUT CAMP

To the Editor: Rhode Island, the littlest state in the Union, has the largest Boy Scout camp in New England. Eight hundred acres are maintained by the Narragansett Council, Boy Scouts of America, as "an Adventure Land forever," tenting between six hundred and seven hundred Boy Scouts a week during July and August.

Usually, these Yankee boys are healthy but occasionally one has an accident or is "upset" in some way or another. The Camp officials are desperately in need of a resident medical officer for the summer. In normal times they employ two men on the medical staff, but this year they have no idea where to secure such assistance. They have tried all the local hospitals, all the hospitals in Greater Boston, the Army and Navy units in and around Narragansett Bay, at Camp Devens and in First and Third Naval Districts, and refugee doctors — they have left no stones unturned.

They now turn to the *Journal* to air their problem over a larger area. Is there not some man who would enjoy eight or nine weeks with kids? There is a beautiful Health Lodge with a treatment room and waiting room, as well as a ward with eight beds, a laboratory and two isolation wards, all modernly equipped. The physician's living quarters are ample for a family.

A tired civilian physician, a discharged medical officer from some branch of the service or someone else ought to be anxious to "do a good turn" for these boys. Anyone who is interested or who has a thought or suggestion is asked to communicate with Mr. H. Cushman Anthony, Narragansett Council, Boy Scouts of America, 26 Custom House Street, Providence 3, Rhode Island, or phone GASpee 9618.

H. Cushman Anthony

26 Custom House Street
Providence 3, Rhode Island

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. Samuel M. Weene, 241 Adams Street, Dorchester, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. William H. H. Briggs, Merrimac, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

DARIER'S DISEASE

To the Editor: Dr. Arthur M. Greenwood has just called to my attention an error on page 367 of the March 23 issue of the *Journal*.

The usual synomym of Darier's disease, at least in the dermatologic world, is keratosis follicularis, not pseudoxanthoma elasticum. It is true that both keratosis follicularis and pseudoxanthoma elasticum were studied by Darier. In the latter disease the name was given it by Darier in 1896, whereas keratosis follicularis was described independently in 1889 by Darier in France and Dr. J. C. White here in Boston. I have heard Dr. C. J. White say several times that the disease should have been named "White's disease" because of his father's contribution.

The description in the *Journal* fits the pseudoxanthoma elasticum all right but it is not what is commonly known as Darier's disease.

C. Guy Lane, M.D.

416 Marlborough Street
Boston 15

Dr. Lane's letter was referred to Dr. Buck, whose reply is as follows:

To the Editor: I am forced to agree that, so far as all immediately available reference works are concerned, the eponym Darier's disease does indeed refer to a variety of keratosis follicularis.

My interest in any individual eponym begins when I hear it used for the first time. I must have been misled by hearing someone refer to a case of pseudoxanthoma elasticum as an example of Darier's disease. To that man and to myself Darier's disease meant pseudoxanthoma elasticum. Between us we must have created a new eponym.

Darier's conclusions regarding follicular keratosis may, I discover, be found in his article "De la psorospermose folliculaire végétante (On Vegetative Follicular Psorospermosis)," which appeared in *Annales de dermatologie et de syphiligraphie* (**10**:597-612, 1889), with a translation from which I herewith make my apologies to the dermatologists:

> There exists in man a group of cutaneous diseases that deserve the name of psorospermoses, since they result from the presence in the epidermis of parasites of the class Sporozoa . . . .
>
> This disease, which may be termed vegetative follicular psorospermosis, should, in consideration of its etiology, be compared to Paget's disease and very probably to molluscum contagiosum.

Robert W. Buck

5 Bay State Road
Boston 15

NOTICES

DIRECTORY OF MEDICAL SPECIALISTS

The third edition of the *Directory of Medical Specialists*, listing names and biographic data of all men certified by the fifteen American boards, is to be published early in 1945. Collection of biographic data of the diplomates certified since the 1942 edition, and revision of the older listings in that volume are now going forward rapidly. Diplomates are requested to make prompt return of notices regarding their biographies as soon as possible after receiving the proper forms from the publication office.

(*Continued on page xi*)

NOTICES (*Continued from page 684*)

ANNOUNCEMENT

Dr. Ora H. Wagman announces the opening of his office for the practice of ophthalmology at 395 Commonwealth Avenue, Boston.

HARVARD MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Harvard Medical Alumni Association will be held at the University Club, 76 East Monroe Street, Chicago, on Wednesday evening, June 14, in association with the meeting of the American Medical Association. Cocktails will be served at 6 p.m., and the dinner is scheduled for 7 p.m. No formal speeches have been arranged, but there will be several informal talks by outstanding graduates.

TUFTS MEDICAL ALUMNI DINNER

The Tufts Medical Alumni will hold a dinner on June 14 in Chicago at the meeting of the American Medical Association. The dinner committee consists of Drs. Harry Olin, of Chicago, and Harry Blotner, co-chairmen, Drs. Carl Bearse, Sara Jordan, Frank R. Ober, Louis E. Phaneuf and Priscilla White.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 8

SATURDAY, JUNE 10

*10:00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, JUNE 12

*12:15-1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, JUNE 13

*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, JUNE 14

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

JUNE 7-13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

JUNE 8-10. American Board of Internal Medicine. Page x, issue of April 20.

JUNE 12-16. American Medical Association. Page 798, issue of November 18.

JUNE 12-16. American Physicians' Art Association. Page x, issue of March 2.

JUNE 14. Harvard Medical Alumni Association. Notice elsewhere on this page.

JUNE 14. Tufts Medical Alumni Dinner. Notice elsewhere on this page.

OCTOBER 3-5. American Public Health Association. Page ix, issue of March 30.

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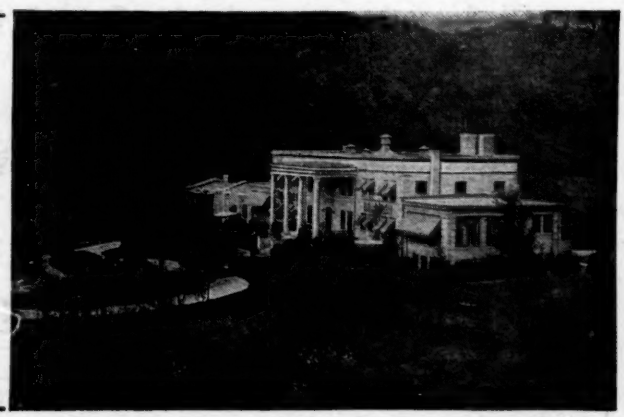

During Food Shortages...

It is well to bear in mind that dried brewers yeast, weight for weight, is the richest food source of the Vitamin B Complex. For example, as little as 1 level teaspoonful (2.5 Gm.) Mead's Brewers Yeast Powder supplies:

45% of the average adult daily thiamine allowance
8% " " " " " riboflavin allowance
10% " " " " " niacin allowance

— in addition to the other factors that occur naturally in yeast such as pyridoxine, pantothenic acid, etc. Following are suggestions for palatably mixing 1 level teaspoonful Mead's Brewers Yeast Powder:

(1) Shake in cocktail shaker with 4 ounces of milk (with or without 1 level teaspoonful sugar and cocoa).

(2) Stir with fork into ¾ ounce of ketchup or chili sauce. Optional, add a few drops of lemon juice.

(3) Stir with fork into 3 ounces of soup (preferably thick soups such as bean, pea, oxtail, beef, etc.).

(4) Spread on bread with 2 to 3 times the amount of peanut butter.

(5) Add 1 level tablespoonful (and a little extra salt) to 2 cups of meat stock gravy.

Mead's Brewers Yeast is supplied in 6-oz. bottles, economically. At the rate of even 2 level teaspoonfuls per day, per adult, a bottle should last over a month. Also supplied in 6-grain tablets. 250 and 1000 tablets per bottle. All Mead Products are advertised only to the medical profession.

Why not try this recipe at home? It makes good gravy taste meatier. Send for tested wartime recipes containing yeast.

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